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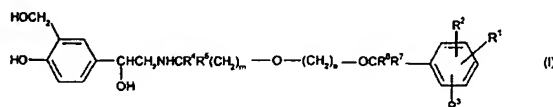
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(54) Title: PHENETHANOLAMINE DERIVATIVES FOR TREATMENT OF RESPIRATORY DISEASES



(57) Abstract: The present invention relates to novel compounds of formula (I), to a process for their manufacture, to pharmaceutical compositions containing them, and to their use in therapy, in particular their use in the prophylaxis and treatment of respiratory diseases.

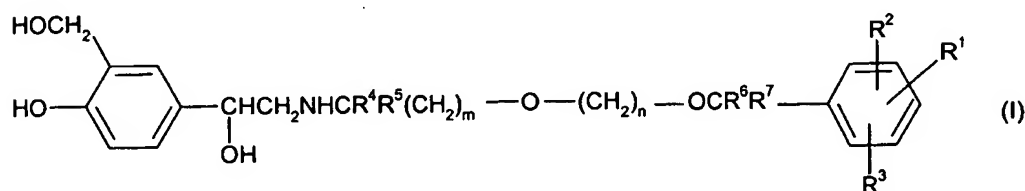
PHENETHANOLAMINE DERIVATIVES FOR TREATMENT OF RESPIRATORY DISEASES

The present invention is concerned with phenethanolamine derivatives, processes for their preparation, compositions containing them and their use in medicine, particularly in the prophylaxis and treatment of respiratory diseases.

Certain phenethanolamine compounds are known in the art as having selective stimulant action at β_2 -adrenoreceptors and therefore having utility in the treatment of bronchial asthma and related disorders. Thus GB 2 140 800 describes phenethanolamine compounds including 4-hydroxy- α^1 -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol 1-hydroxy-2-naphthalenecarboxylate (salmeterol xinafoate) which is now used clinically in the treatment of such medical conditions.

Although salmeterol and the other commercially available β_2 -adrenoreceptor agonists are effective bronchodilators, the maximum duration of action is 12 hours, hence twice daily dosing is often required. There is therefore a clinical need for compounds having potent and selective stimulant action at β_2 -adrenoreceptors and having an advantageous profile of action.

According to the present invention, there is provided a compound of formula (I)



or a salt, solvate, or physiologically functional derivative thereof, wherein:

m is an integer of from 2 to 8;

n is an integer of from 2 to 5;

with the proviso that m + n is 4 to 10;

R¹ is selected from hydrogen, C₁₋₆alkyl, hydroxy, halo, C₁₋₆haloalkyl, -XC(O)NR⁹R¹⁰, -XNR⁸C(O)R⁹, -XNR⁸C(O)NR⁹R¹⁰, -XNR⁸SO₂R⁹, -XSO₂NR¹¹R¹², XNR⁸SO₂R⁹R¹⁰, -XNR⁹R¹⁰, XN⁺R⁸R⁹R¹⁰, -XNR⁸C(O)OR⁹, -XCO₂R⁹, -XNR⁸C(O)NR⁸C(O)NR⁹R¹⁰, -XSR⁹, XSOR⁹, and -XSO₂R⁹;

- 5 or R¹ is selected from -X-aryl, -X-hetaryl, and -X-(aryloxy), each optionally substituted by 1 or 2 groups independently selected from hydroxy, C₁₋₆alkoxy, halo, C₁₋₆alkyl, C₁₋₆haloalkyl, -NHC(O)(C₁₋₆alkyl), -SO₂(C₁₋₆alkyl), -SO₂(aryl), -SO₂NH₂, -SO₂NH(C₁₋₆alkyl), -SO₂NH(C₃₋₇cycloalkyl), -CO₂H, -CO₂(C₁₋₆alkyl), -SO₂NH(C₃₋₇cycloalkylC₁₋₆alkyl), -NH₂, -NH(C₁₋₆alkyl), or hetaryl optionally substituted by
- 10 1 or 2 groups independently selected from hydroxy, C₁₋₆alkoxy, halo, C₁₋₆alkyl, or C₁₋₆haloalkyl;

X is -(CH₂)_p- or C₂₋₆ alkenylene;

- 15 p is an integer from 0 to 6, preferably 0 to 4;

- R⁸ and R⁹ are independently selected from hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, aryl, hetaryl, hetaryl(C₁₋₆alkyl)- and aryl(C₁₋₆alkyl)- and R⁸ and R⁹ are each independently optionally substituted by 1 or 2 groups independently selected from halo, C₁₋₆alkyl,
- 20 C₁₋₆haloalkyl, -NHC(O)(C₁₋₆alkyl), -SO₂(C₁₋₆alkyl), -SO₂(aryl), -CO₂H, -CO₂(C₁₋₄alkyl), -NH₂, -NH(C₁₋₆alkyl), aryl(C₁₋₆alkyl)-, aryl(C₂₋₆alkenyl)-, aryl(C₂₋₆alkynyl)-, hetaryl(C₁₋₆alkyl)-, -NHSO₂aryl, -NH(hetarylC₁₋₆alkyl), -NHSO₂hetaryl, -NHSO₂(C₁₋₆alkyl), -NHC(O)aryl, or -NHC(O)hetaryl:

- 25 R¹⁰ is selected from hydrogen, C₁₋₆alkyl and C₃₋₇ cycloalkyl;

- R¹¹ and R¹² are independently selected from hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, aryl, hetaryl, hetaryl(C₁₋₆alkyl)- and aryl(C₁₋₆alkyl)-, or R¹¹ and R¹², together with the nitrogen to which they are bonded, form a 5-, 6-, or 7- membered nitrogen containing ring;
- 30 and R¹¹ and R¹² are each optionally substituted by one or two groups independently selected from halo, C₁₋₆alkyl, and C₁₋₆haloalkyl;

where R¹ is -XNR⁸C(O)NR⁹R¹⁰, R⁸ and R⁹ may, together with the -NC(O)N- portion of the group R¹ to which they are bonded, form a saturated or unsaturated ring, preferably

a 5-, 6-, or 7- membered ring, for example an imidazolidine or pyrimidine ring, such as imidazolidine-2,4-dione or pyrimidine -2, 4-dione;

5 where R¹ is -XNR⁸C(O)OR⁹, R⁸ and R⁹ may, together with the -NC(O)O- portion of the group R¹ to which they are bonded, form a saturated or unsaturated ring, preferably a 5-, 6-, or 7- membered ring, for example an oxazolidine ring, such as oxazolidine-2,4-dione;

10 where R¹ is -XC(O)NR⁹R¹⁰ or -XNR⁸C(O)NR⁹R¹⁰, R⁸ and R¹⁰ may, together with the nitrogen to which they are bonded, form a 5-, 6-, or 7- membered nitrogen containing ring;

R² is selected from hydrogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, halo, aryl, aryl(C₁₋₆alkyl)-, C₁₋₆haloalkoxy, and C₁₋₆ haloalkyl;

15 R³ is selected from hydrogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, halo, aryl, aryl(C₁₋₆alkyl)-, C₁₋₆haloalkoxy, and C₁₋₆haloalkyl;

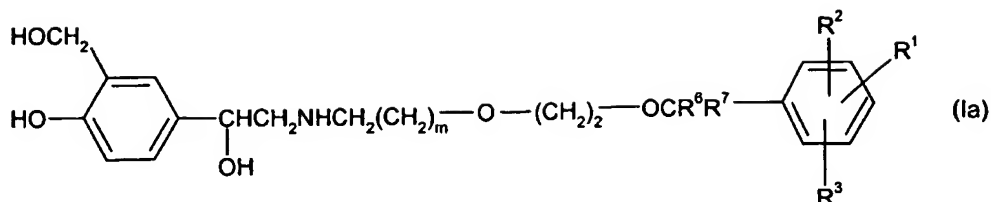
20 R⁴ and R⁵ are independently selected from hydrogen and C₁₋₄ alkyl with the proviso that the total number of carbon atoms in R⁴ and R⁵ is not more than 4; and,

R⁶ and R⁷ are independently selected from hydrogen and C₁₋₄alkyl with the proviso that the total number of carbon atoms in R⁴ and R⁵ is not more than 4.

25 In the compounds of formula (I) and (Ia), R⁶ and R⁷ are preferably independently selected from hydrogen and methyl, more preferably R⁶ and R⁷ are both hydrogen.

In the compounds of formula (I), m is suitably 4, 5 or 6, more suitably 4 or 5 and preferably 5 and n is suitably 2 or 3 and preferably n is 2.

30 According to a preferred aspect of the invention, there is provided a compound of formula (Ia)



- 5 or a salt, solvate, or physiologically functional derivative thereof, wherein R^1 , R^2 , R^3 , R^6 and R^7 are as defined above for formula (I) and m is 4 or 5.

10 In the compounds of formulae (I) and (Ia), the group R^1 is preferably attached to the para- or meta-position, and more preferably to the meta-position relative to the $-OCR^6R^7$ - link. The groups R^2 and R^3 are each independently preferably attached to the ortho- or meta- position, more preferably to the ortho position relative to the $-OCR^6R^7$ - link.

15 In one preferred embodiment R^1 represents a substituent as defined above, other than hydrogen, most preferably attached to the meta-position relative to the $-OCR^6R^7$ -link, and R^2 and R^3 each represent hydrogen.

20 In another preferred embodiment R^1 represents hydrogen and R^2 and R^3 each represent a substituent as defined above, at least one of which is other than hydrogen, and R^2 and R^3 are each independently attached to the ortho- or meta- positions relative to the $-OCR^6R^7$ -link. In a particular embodiment, when R^2 and R^3 each represent halogen they are preferably attached at the ortho positions and when R^2 and R^3 each represent methyl they are preferably attached at the meta positions.

25 In the compounds of formulae (I) and (Ia) R^1 is suitably selected from hydrogen, C_{1-6} alkyl, hydroxy, halo, C_{1-6} haloalkyl, $-XNR^8(C)OR^9$, $-XNR^8C(O)NR^9R^{10}$, $-XNR^8SO_2R^9$, $-XSO_2NR^{11}R^{12}$, $-XNR^9R^{10}$, $-XNR^8C(O)OR^9$, XSR^9 , $XSOR^9$, XSO_2R^9 , or from X-aryl, X-hetaryl or X-aryloxy, optionally substituted as defined above.

X is suitably $(CH_2)_p$ wherein p is preferably zero.

R^8 and R^{10} suitably represent hydrogen.

5 R^9 suitably represents hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, hetaryl or hetaryl(C_{1-6} alkyl)-, any of which may be optionally substituted by C_{1-6} alkyl, C_{1-6} haloalkyl, $-SO_2(C_{1-6}$ alkyl), NH_2 , aryl (C_{1-6} alkyl), aryl(C_{2-6} alkynyl), $NHSO_2$ aryl, $-NH$ (hetaryl(C_{1-6} alkyl), $NHC(O)$ aryl or $NHC(O)$ hetaryl).

10 R^{11} and R^{12} are suitably each independently selected from hydrogen, C_{1-6} alkyl and C_{3-7} cycloalkyl.

In the definition of R^1 , the term "5-, 6-, or 7- membered nitrogen containing ring" means a 5-, 6-, or 7- membered saturated or unsaturated ring which includes a nitrogen atom
15 and optionally 1 or 2 other heteroatoms independently selected from nitrogen, sulphur, and oxygen. Suitable examples of such a ring include piperidinyl, morpholinyl, pyridyl, 2,4-dihydropyrimidinyl, and piperazinyl.

In the definition of R^1 , the term "hetaryl" means a 5- to 10- membered heteroaromatic
20 ring or bicyclic ring system which includes 1, 2, or 3 heteroatoms independently selected from oxygen, nitrogen and sulphur, such as thienyl, pyridyl, 2,4-dihydropyrimidinyl, 2,3-dihydroimidazo[2,1-b][1,3]thiazol-6-yl, or bipyridyl, preferably a 5- or 6-membered heteroaromatic ring.

25 As used herein, the term "aryl" either alone or in the term "aryloxy" means a monocyclic or bicyclic aromatic ring system, such as phenyl, naphthyl, or biphenyl. Preferably the term "aryl" means phenyl.

In the compounds of formulae (I) and (Ia), the group R^1 is preferably selected from
30 hydrogen, C_{1-4} alkyl, hydroxy, halo, $-NR^8C(O)NR^9R^{10}$, and $-NR^8SO_2R^9$ wherein R^8 and R^9 are as defined above or more suitably wherein R^8 is hydrogen and R^9 is selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, and aryl and is optionally substituted as described above.

In the compounds of formulae (I) and (Ia) wherein the group R¹ is substituted by R⁸ and/or R¹⁰, R⁸ and/or R¹⁰ are suitably hydrogen.

5 In the compounds of formula (I) and (Ia) R² and R³ are preferably independently selected from hydrogen, halogen (eg. fluorine or more preferably chlorine), halo C₁₋₆alkyl (eg. CF₃), C₁₋₆alkyl (eg. methyl) and phenyl or substituted phenyl (eg. p-methoxyphenyl).

10 In the compounds of formula (I), R⁴ and R⁵ are preferably independently selected from hydrogen and methyl, more preferably R⁴ and R⁵ are both hydrogen.

It is to be understood that the present invention covers all combinations of particular and preferred groups described hereinabove.

15 Preferred compounds of the invention include:

N-{3-[(2-{[6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino)hexyl]oxy}ethoxy)methyl]phenyl}-N'-phenylurea;
4-[(1R)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl]-2-(hydroxymethyl)phenol;

20 N-(1,1'-biphenyl-4-yl)-N'-{3-[(2-{[6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl]oxy}ethoxy)methyl]phenyl}urea;

N-cyclohexyl-N'-{3-[(2-{[6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl]oxy}ethoxy)methyl]phenyl}urea;

25 4-[(1R)-2-[(6-{2-(benzyloxy)ethoxy}hexyl)amino]-1-hydroxyethyl]-2-(hydroxymethyl)phenol;

4-[(2-{[6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)-hexyl]oxy}ethoxy)methyl]benzenesulfonamide;

4-[(1R)-1-hydroxy-2-[(6-{2-[(4-iodobenzyl)oxy]ethoxy}hexyl)amino]ethyl]-2-(hydroxymethyl)phenol;

30 3-[(2-{[6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)-hexyl]oxy}ethoxy)methyl]benzenesulfonamide;

2-(hydroxymethyl)-4-[(1R)-1-hydroxy-2-[(6-{2-[(1R)-1-phenylethyl]oxy}ethoxy)-hexyl]amino]ethyl]phenol;

2-(hydroxymethyl)-4-[(1R)-1-hydroxy-2-[(6-{2-[(1S)-1-phenylethyl]oxy}ethoxy)-hexyl]amino]ethyl]phenol;

35

- 4-((1R)-2-((6-(2-((4-chlorobenzyl)oxy)ethoxy)hexyl)amino)-1-hydroxyethyl)-2-(hydroxymethyl)phenol;
 2-(hydroxymethyl)-4-((1R)-1-hydroxy-2-((6-(2-((4-methylbenzyl)oxy)ethoxy)hexyl)amino)ethyl)phenol;
 5 4-((1R)-2-((6-(2-((2,4-dichlorobenzyl)oxy)ethoxy)hexyl)amino)-1-hydroxyethyl)-2-(hydroxymethyl)phenol;
 2-(hydroxymethyl)-4-((1R)-1-hydroxy-2-((6-(2-((4-(trifluoromethyl)benzyl)oxy)ethoxy)hexyl)amino)ethyl)phenol;
 10 4-((1R)-1-hydroxy-2-((6-(2-((3-hydroxybenzyl)oxy)ethoxy)hexyl)amino)ethyl)-2-(hydroxymethyl)phenol;
 N-3-((2-((6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino)hexyl)oxy)ethoxy)methyl)phenyl)urea;
 N-3-((2-((6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl)oxy)ethoxy)methyl)phenyl)-4-
 15 (methylsulfonyl)benzenesulfonamide;
 N-3-((2-((6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino)hexyl)oxy)ethoxy)methyl)phenyl)methanesulfonamide;
 N-3-(((3-((2-((6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino)hexyl)oxy)ethoxy)methyl)phenyl)amino)carbonyl)amino)phenyl)pyridine-3-
 20 carboxamide;
 N-(3-ethylphenyl)-N'-3-((2-((6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl)oxy)ethoxy)methyl)phenyl)urea;
 N-3-((2-((6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl)oxy)ethoxy)methyl)phenyl)-N'-(3-methylphenyl)urea;
 25 N-3-((2-((6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino)hexyl)oxy)ethoxy)methyl)phenyl)-N'-(3-(trifluoromethyl)phenyl)urea;
 N-(3,5-dichlorophenyl)-N'-2-((2-((6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl)oxy)ethoxy)methyl)phenyl)urea;
 N-(3-chlorophenyl)-N'-3-((2-((6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl)oxy)ethoxy)methyl)phenyl)urea;
 30 N-3-((2-((6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl)oxy)ethoxy)methyl)phenyl)-N'-(3-iodophenyl)urea;
 4-((1R)-2-((6-(2-((3-aminobenzyl)oxy)ethoxy)hexyl)amino)-1-hydroxyethyl)-2-(hydroxymethyl)phenol;

- N-{3-[(2-[(6-[(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino]hexyl]oxy)ethoxy)methyl]phenyl}pyridine-3-carboxamide;
N-{3-[(2-[(6-[(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino]hexyl]oxy)ethoxy)methyl]phenyl}thiophene-2-carboxamide;
5 N-{3-[(2-[(6-[(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino]hexyl]oxy)ethoxy)methyl]phenyl}benzamide;
3-(benzoylamino)-N-{3-[(2-[(6-[(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino]hexyl]oxy)ethoxy)methyl]phenyl}benzamide;
N-{3-[(3-[(2-[(6-[(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino]hexyl]oxy)ethoxy)methyl]phenyl)amino)carbonyl]phenyl}thiophene-2-
10 carboxamide;
N-{3-[(3-[(2-[(6-[(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino]hexyl]oxy)ethoxy)methyl]phenyl)amino)carbonyl]phenyl}nicotinamide;
N-{3-[(3-[(2-[(6-[(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino]hexyl]oxy)ethoxy)methyl]phenyl)amino)carbonyl]amino}phenyl)-
15 benzenesulfonamide;
4-[(1R)-2-[(6-[2-(1,1'-biphenyl-2-ylmethoxy)ethoxy]hexyl)amino]-1-hydroxyethyl]-2-(hydroxymethyl)phenol;
4-[(1R)-1-hydroxy-2-[(6-[2-[(4'-methoxy-1,1'-biphenyl-2-yl)methoxy]ethoxy)-hexyl]amino]ethyl]-2-(hydroxymethyl)phenol;
20 4-[(1R)-2-[(6-[2-[(3-bromobenzyl)oxy]ethoxy]hexyl)amino]-1-hydroxyethyl]-2-(hydroxymethyl)phenol;
2-(hydroxymethyl)-4-[(1R)-1-hydroxy-2-[(6-[2-[(3-phenoxybenzyl)oxy]ethoxy)-hexyl]amino]ethyl]phenol;
25 4-[(1R)-1-hydroxy-2-[(6-[2-[(4-hydroxybenzyl)oxy]ethoxy]hexyl)amino]ethyl]-2-(hydroxymethyl)phenol;
5-{3-[(2-[(6-[(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino]hexyl]oxy)ethoxy)methyl]phenyl}pyrimidine-2,4-diol;
4-[(1R)-2-[(6-[2-[(2,5-dichlorobenzyl)oxy]ethoxy]hexyl)amino]-1-hydroxyethyl]-2-
30 (hydroxymethyl)phenol;
4-[(1R)-2-[(6-[2-[(3,5-dimethylbenzyl)oxy]ethoxy]hexyl)amino]-1-hydroxyethyl]-2-(hydroxymethyl)phenol;
4-[(1R)-2-[(6-[2-[(2-fluoro-6-(trifluoromethyl)benzyl)oxy]ethoxy]hexyl)amino]-1-hydroxyethyl]-2-(hydroxymethyl)phenol;

- 2-(hydroxymethyl)-4-((1R)-1-hydroxy-2-((6-(2-((3-(trifluoromethoxy)benzyl)-oxy)ethoxy)hexyl)amino)ethyl)phenol;
- 2-(hydroxymethyl)-4-((1R)-1-hydroxy-2-((6-(2-((2-methyl-1,1'-biphenyl-3-yl)methoxy)ethoxy)hexyl)amino)ethyl)phenol;
- 5 3-((2,3-dihydroimidazo[2,1-b][1,3]thiazol-6-ylmethyl)amino)-N-{3-((2-((6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl)oxy)ethoxy)-methyl)phenyl)benzamide;
- N-{3-(((3-((2-((6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl)oxy)ethoxy)methyl)phenyl)amino)carbonyl)amino)phenyl)benzamide;
- 10 N-{3-(((3-((2-((6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino)hexyl)oxy)ethoxy)methyl)phenyl)amino)carbonyl)amino)phenyl)thiophene-2-carboxamide;
- N-(1,1'-biphenyl-3-yl)-N'-{3-((2-((6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl)oxy)ethoxy)methyl)phenyl)urea;
- 15 N-(3-aminophenyl)-N'-{3-((2-((6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl)oxy)ethoxy)methyl)phenyl)urea;
- 3-((2-((6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)-hexyl)oxy)ethoxy)methyl)-N-methylbenzenesulfonamide;
- 20 N-{3-((2-((6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino)hexyl)oxy)ethoxy)methyl)phenyl)-3-((thien-2-ylsulfonyl)amino)benzamide;
- N-{3-((2-((6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl)oxy)ethoxy)methyl)phenyl)-N'-[3-(2-phenylethyl)-phenyl]urea;
- 25 cyclopentyl 3-((2-((6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl)oxy)ethoxy)methyl)phenyl)carbamate;
- 5-{3'-((2-((6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl)oxy)ethoxy)methyl)-1,1'-biphenyl-3-yl}pyrimidine-2,4(1H,3H)-dione;
- 4-((1R)-1-hydroxy-2-((6-(2-((3-iodobenzyl)oxy)ethoxy)hexyl)amino)-ethyl)-2-(hydroxymethyl)phenol;
- 30 3'-((2-((6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl)oxy)ethoxy)methyl)-1,1'-biphenyl-3-ol;
- N-cyclohexyl-3-((2-((6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl)oxy)ethoxy)methyl)benzenesulfonamide;

- N-{3-[(2-[[6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)-phenyl]ethyl)-amino)hexyl]oxy}ethoxy)methyl]phenyl)-3-[(phenylsulfonyl)amino]benzamide;
 4-[(1R)-2-[[6-2-[(3-[(2,3-dihydroimidazo[2,1-b][1,3]thiazol-6-ylmethyl)amino]-benzyl]oxy}ethoxy]hexyl]amino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol;
 5 N-cyclopropyl-3'-[(2-[[6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxy-methyl)-phenyl]ethyl)amino)hexyl]oxy}ethoxy)methyl]-1,1'-biphenyl-2-sulfonamide;
 N-{3-[(2-[[6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)-phenyl]ethyl)-amino)hexyl]oxy}ethoxy)methyl]phenyl)-N'-[3-(phenylethynyl)phenyl]urea;
 N-{3-[(2-[[5-(((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)pentyl]oxy}ethoxy)methyl]phenyl)-N-phenylurea;
 10 N-{3-[(3-[[5-(((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)pentyl]oxy}propoxy)methyl]phenyl)-N-phenylurea;
 N-{3-[(2-[[7-(((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)heptyl]oxy}ethoxy)methyl]phenyl)-N-phenylurea;
 15 N-(3-[[[3-[(2-[[5-(((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)pentyl]oxy}ethoxy)methyl]phenyl]amino)carbonyl]amino)phenyl)nicotinamide;
 N-(3-[[[3-[(3-[[5-(((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)pentyl]oxy}propoxy)methyl]phenyl]amino)carbonyl]amino)phenyl)nicotinamide;
 20 N-(3-[[[3-[(3-[[7-(((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)heptyl]oxy}propoxy)methyl]phenyl]amino)carbonyl]amino)phenyl)nicotinamide;
 N-(3-[(2-[[5-(((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)pentyl]oxy}ethoxy)methyl]phenyl)methanesulfonamide;
 25 N-(3-[(3-[[5-(((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)pentyl]oxy}prop)amino)methyl]phenyl)methanesulfonamide;
 N-(3-[(2-[[7-(((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)heptyl]oxy}ethoxy)methyl]phenyl)methanesulfonamide;
 30 N-(3-[(2-[[6-(((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl]oxy}ethoxy)methyl]phenyl)benzenesulfonamide;
 4-((1R)-2-[[6-2-[(3-(Dimethylamino)benzyl]oxy}ethoxy)hexyl]amino)-1-hydroxyethyl)-2-(hydroxymethyl)phenol;

3-[(2-[(6-((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl]oxy)ethoxy)methyl]-N,N,N-trimethylbenzenaminium;

5 N-[4-[(2-[(6-((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl]oxy)ethoxy)methyl]phenyl]-N'-phenylurea;
4-[(1R)-2-[(5-[2-[(2,6-dichlorobenzyl)oxy]ethoxy)pentyl]amino]-1-hydroxyethyl]-2-(hydroxymethyl)phenol;

and salts, solvates, and physiologically functional derivatives thereof.

10

Particularly preferred compounds of the invention include:

N-[3-[(2-[(6-((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino)hexyl]oxy)ethoxy)methyl]phenyl]-N'-phenylurea;

15 4-[(1R)-2-[(6-[2-[(2,6-dichlorobenzyl)oxy]ethoxy)hexyl]amino]-1-hydroxyethyl]-2-(hydroxymethyl)phenol;

N-[3-[[[3-[(2-[(6-((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino)hexyl]oxy)ethoxy)methyl]phenyl]amino)carbonyl]amino]phenyl]pyridine-3-carboxamide;

20 4-[(1R)-1-Hydroxy-2-[(6-[2-[(3-hydroxybenzyl)oxy]ethoxy)hexyl]amino]ethyl]-2-(hydroxymethyl)phenol;

4-[(1R)-2-[(6-[2-[(3,5-Dimethylbenzyl)oxy]ethoxy)hexyl]amino]-1-hydroxyethyl]-2-(hydroxymethyl)phenol;

N-[3-[(2-[(5-((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino)pentyl]oxy)ethoxy)methyl]phenyl]-N'-phenylurea;

25

and salts, solvates, and physiologically functional derivatives thereof.

Particularly preferred compounds of the invention further include:

30 4-[(1R)-2-[(6-[2-[(2,6-dichlorobenzyl)oxy]ethoxy)hexyl]amino]-1-hydroxyethyl]-2-(hydroxymethyl)phenol;

and salts and solvates thereof.

The compounds of formulae (I) and (Ia) include an asymmetric centre, namely the carbon atom of the



- 5 group. The present invention includes both (S) and (R) enantiomers either in substantially pure form or admixed in any proportions.

- 10 Similarly, where R^4 and R^5 are different groups or where R^6 and R^7 are different groups, the carbon atom to which they are attached is an asymmetric centre and the present invention includes both (S) and (R) isomers at these centres either in substantially pure form or admixed in any proportions.

- 15 Thus the compounds of formulae (I) and (Ia) include all enantiomers and diastereoisomers as well as mixtures thereof in any proportions.

- 20 Salts and solvates of compounds of formulae (I) and (Ia) which are suitable for use in medicine are those wherein the counterion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counterions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of formulae (I) and (Ia) and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives.

- 25 By the term "physiologically functional derivative" is meant a chemical derivative of a compound of formula (I) or (Ia) having the same physiological function as the free compound of formula (I) or (Ia), for example, by being convertible in the body thereto. According to the present invention, examples of physiologically functional derivatives include esters.

- 30 Pharmaceutically acceptable esters of the compounds of formula (I) and (Ia) may have a hydroxyl group converted to a C_{1-6} alkyl, aryl, C_{1-6} alkyl, or amino acid ester.

Suitable salts according to the invention include those formed with both organic and inorganic acids or bases. Pharmaceutically acceptable acid addition salts include those

formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, triphenylacetic, phenylacetic, substituted phenyl acetic eg. methoxyphenyl acetic, sulphamic, sulphanilic, succinic, oxalic, fumaric, maleic, malic, glutamic, aspartic, oxaloacetic, methanesulphonic, ethanesulphonic, arylsulponic
5 (for example p-toluenesulphonic, benzenesulphonic, naphthalenesulphonic or naphthalenedisulphonic), salicylic, glutaric, gluconic, tricarballic, mandelic, cinnamic, substituted cinnamic (for example, methyl, methoxy, halo or phenyl substituted cinnamic, including 4-methyl and 4-methoxycinnamic acid and α -phenyl cinnamic acid), ascorbic, oleic, naphthoic, hydroxynaphthoic (for example 1- or 3-hydroxy-2-naphthoic),
10 naphthaleneacrylic (for example naphthalene-2-acrylic), benzoic, 4-methoxybenzoic, 2- or 4-hydroxybenzoic, 4-chlorobenzoic, 4-phenylbenzoic, benzenecrylic (for example 1,4-benzenediacrylic) and isethionic acids. Pharmaceutically acceptable base salts include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium and salts with organic bases
15 such as dicyclohexyl amine and N-methyl-D-glucamine.

Advantageously, preferred compounds of the invention such as 4-((1*R*)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl)-2-(hydroxymethyl)phenol
20 are provided in the form of a crystalline salt, for example selected from those exemplified in the experimental section below. Said crystalline salts have favourable physical properties such as low hygroscopicity and/or improved stability.

As mentioned above, the compounds of formulae (I) and (Ia) are selective β_2 -adrenoreceptor agonists as demonstrated using functional or reporter gene readout
25 from cell lines transfected with human beta-adrenoreceptors as described below. Compounds according to the present invention also have the potential to combine long duration of effect with rapid onset of action. Furthermore, certain compounds have shown an improved therapeutic index in animal models relative to existing long-acting β_2 -agonist bronchodilators. In addition, compounds of the invention demonstrate
30 pharmacokinetic properties that will reduce systemic exposure relative to existing long-acting beta2 agonist bronchodilators. As such, compounds of the invention may be suitable for once-daily administration.

Therefore, compounds of formulae (I) and (Ia) and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives have use in the prophylaxis and treatment of clinical conditions for which a selective β_2 -adrenoreceptor agonist is indicated. Such conditions include diseases associated with reversible airways
5 obstruction such as asthma, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease (eg. rhinitis, including seasonal and allergic rhinitis).

Other conditions which may be treated include premature labour, depression,
10 congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) and muscle wasting disease.

Accordingly, the present invention provides a method for the prophylaxis or treatment of
15 a clinical condition in a mammal, such as a human, for which a selective β_2 -adrenoreceptor agonist is indicated, which comprises administration of a therapeutically effective amount of a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof. In particular, the present invention provides such a method for the prophylaxis or treatment of a disease
20 associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease. In a further aspect the present invention provides such a method for the prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin
25 diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) or muscle wasting disease.

In the alternative, there is also provided a compound of formula (I) or (Ia) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof
30 for use in medical therapy, particularly, for use in the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2 -adrenoreceptor agonist is indicated. In particular, there is provided a compound of formula (I) or (Ia) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for the prophylaxis or treatment of a disease associated
35 with reversible airways obstruction such as asthma, chronic obstructive pulmonary

disease (COPD), respiratory tract infection or upper respiratory tract disease. In a further aspect, there is provided a compound of formula (I) or (Ia) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for the prophylaxis or treatment of a clinical condition selected from premature labour,
5 depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) or muscle wasting disease.

The present invention also provides the use of a compound of formula (I) or (Ia), or a
10 pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a selective β_2 -adrenoreceptor agonist is indicated, for example a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory
15 tract disease. In a further aspect, there is provided a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases),
20 conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) and muscle wasting disease.

The amount of a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof which is required to achieve a
25 therapeutic effect will, of course, vary with the particular compound, the route of administration, the subject under treatment, and the particular disorder or disease being treated. The compounds of the invention may be administered by inhalation at a dose of from 0.0005mg to 10 mg, preferably 0.005mg to 0.5mg. The dose range for adult humans is generally from 0.0005 mg to 100mg per day and preferably 0.01 mg to 1mg
30 per day.

While it is possible for the compound of formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to be administered alone, it is preferable to present it as a pharmaceutical formulation.

Accordingly, the present invention further provides a pharmaceutical formulation comprising a compound of formula (I) or (Ia) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

5

The compounds and pharmaceutical formulations according to the invention may be used in combination with or include one or more other therapeutic agents, for example anti-inflammatory agents, anticholinergic agents (particularly an M_1 , M_2 , M_1/M_2 or M_3 receptor antagonist), other β_2 -adrenoreceptor agonists, antiinfective agents (e.g. antibiotics, antivirals), or antihistamines. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with one or more other therapeutically active agents, for example, an anti-inflammatory agent (for example a corticosteroid or an NSAID), an anticholinergic agent, another β_2 -adrenoreceptor agonist, an antiinfective agent (e.g. an antibiotic or an antiviral), or an antihistamine. Preferred are combinations comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a corticosteroid, and/or an anticholinergic, and/or a PDE-4 inhibitor. Preferred combinations are those comprising one or two other therapeutic agents.

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It will be clear to a person skilled in the art that, where appropriate, the other therapeutic ingredient(s) may be used in the form of salts, (e.g. as alkali metal or amine salts or as acid addition salts), or prodrugs, or as esters (e.g. lower alkyl esters), or as solvates (e.g. hydrates) to optimise the activity and/or stability and/or physical characteristics (e.g. solubility) of the therapeutic ingredient. It will be clear also that where appropriate, the therapeutic ingredients may be used in optically pure form.

30

Suitable anti-inflammatory agents include corticosteroids and NSAIDs. Suitable corticosteroids which may be used in combination with the compounds of the invention are those oral and inhaled corticosteroids and their pro-drugs which have anti-inflammatory activity. Examples include methyl prednisolone, prednisolone, dexamethasone, fluticasone propionate, $6\alpha,9\alpha$ -difluoro- 17α -[(2-furanylcarbonyl)oxy]- 11β -hydroxy- 16α -methyl-3-oxo-androsta-1,4-diene- 17β -carbothioic acid S-fluoromethyl

- ester, 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxy- androsta-1,4-diene-17 β -carbothioic acid *S*-(2-oxo-tetrahydro-furan-3*S*-yl) ester, 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-17 α -[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17 β -carbothioic acid *S*-fluoromethyl ester, beclomethasone esters (e.g. the 17-propionate ester or the 17,21-dipropionate ester), budesonide, flunisolide, mometasone esters (e.g. the furoate ester), triamcinolone acetonide, rofleponide, ciclesonide, butixocort propionate, RPR-106541, and ST-126. Preferred corticosteroids include fluticasone propionate, and 6 α ,9 α -difluoro-17 α -[(2-furanylcarbonyl)oxy]-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid *S*-fluoromethyl ester and
- 10 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-17 α -[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17 β -carbothioic acid *S*-fluoromethyl ester, more preferably 6 α ,9 α -difluoro-17 α -[(2-furanylcarbonyl)oxy]-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid *S*-fluoromethyl ester.
- 15 Suitable NSAIDs include sodium cromoglycate, nedocromil sodium, phosphodiesterase (PDE) inhibitors (e.g. theophylline, PDE4 inhibitors or mixed PDE3/PDE4 inhibitors), leukotriene antagonists, inhibitors of leukotriene synthesis, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine receptor agonists or antagonists (e.g. adenosine 2a agonists), cytokine antagonists (e.g. chemokine
- 20 antagonists) or inhibitors of cytokine synthesis. Suitable other β_2 -adrenoreceptor agonists include salmeterol (e.g. as the xinafoate), salbutamol (e.g. as the sulphate or the free base), formoterol (e.g. as the fumarate), fenoterol or terbutaline and salts thereof.
- 25 Of particular interest is use of the compound of formula (I) in combination with a phosphodiesterase 4 (PDE4) inhibitor or a mixed PDE3/PDE4 inhibitor. The PDE4-specific inhibitor useful in this aspect of the invention may be any compound that is known to inhibit the PDE4 enzyme or which is discovered to act as a PDE4 inhibitor, and which are only PDE4 inhibitors, not compounds which inhibit other members of the
- 30 PDE family as well as PDE4. Generally it is preferred to use a PDE4 inhibitor which has an IC₅₀ ratio of about 0.1 or greater as regards the IC₅₀ for the PDE4 catalytic form which binds rolipram with a high affinity divided by the IC₅₀ for the form which binds rolipram with a low affinity. For the purposes of this disclosure, the cAMP catalytic site

which binds R and S rolipram with a low affinity is denominated the "low affinity" binding site (LPDE 4) and the other form of this catalytic site which binds rolipram with a high affinity is denominated the "high affinity" binding site (HPDE 4). This term "HPDE4" should not be confused with the term "hPDE4" which is used to denote human PDE4.

- 5 Initial experiments were conducted to establish and validate a [^3H]-rolipram binding assay. Details of this work are given in the Binding Assays described in detail below.

The preferred PDE4 inhibitors for use in this invention will be those compounds which have a salutary therapeutic ratio, i.e., compounds which preferentially inhibit cAMP
10 catalytic activity where the enzyme is in the form that binds rolipram with a low affinity, thereby reducing the side effects which apparently are linked to inhibiting the form which binds rolipram with a high affinity. Another way to state this is that the preferred compounds will have an IC_{50} ratio of about 0.1 or greater as regards the IC_{50} for the PDE4 catalytic form which binds rolipram with a high affinity divided by the IC_{50} for the
15 form which binds rolipram with a low affinity.

A further refinement of this standard is that of one wherein the PDE4 inhibitor has an IC_{50} ratio of about 0.1 or greater; said ratio is the ratio of the IC_{50} value for competing with the binding of 1nM of [^3H]R-rolipram to a form of PDE4 which binds rolipram with a
20 high affinity over the IC_{50} value for inhibiting the PDE4 catalytic activity of a form which binds rolipram with a low affinity using 1 μM [^3H]-cAMP as the substrate.

Examples of useful PDE4 inhibitors are:

- (R)-(+)-1-(4-bromobenzyl)-4-[(3-cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidone;
25 (R)-(+)-1-(4-bromobenzyl)-4-[(3-cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidone;
3-(cyclopentyloxy-4-methoxyphenyl)-1-(4-N'-[N2-cyano-S-methyl-isothioureido]benzyl)-
2-pyrrolidone;
cis 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylic acid];
cis-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol];
30 (R)-(+)-ethyl [4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidine-2-ylidene]acetate; and
(S)-(-)-ethyl [4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidine-2-ylidene]acetate.

Most preferred are those PDE4 inhibitors which have an IC₅₀ ratio of greater than 0.5, and particularly those compounds having a ratio of greater than 1.0. Preferred compounds are *cis* 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylic acid, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-

5 difluoromethoxyphenyl)cyclohexan-1-one and *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol]; these are examples of compounds which bind preferentially to the low affinity binding site and which have an IC₅₀ ratio of 0.1 or greater.

10 Other compounds of interest include:

Compounds set out in U.S. patent 5,552,438 issued 03 September, 1996; this patent and the compounds it discloses are incorporated herein in full by reference. The compound of particular interest, which is disclosed in U.S. patent 5,552,438, is *cis*-4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid (also

15 known as cilomalast) and its salts, esters, pro-drugs or physical forms;

AWD-12-281 from Asta Medica (Hofgen, N. et al. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.98; CAS reference No. 247584020-9); a 9-benzyladenine derivative nominated NCS-613 (INSERM); D-4418 from Chiroscience and Schering-Plough; a benzodiazepine PDE4 inhibitor identified as CI-1018 (PD-

20 168787) and attributed to Pfizer; a benzodioxole derivative disclosed by Kyowa Hakko in WO99/16766; K-34 from Kyowa Hakko; V-11294A from Napp (Landells, L.J. et al. Eur Resp J [Annu Cong Eur Resp Soc (Sept 19-23, Geneva) 1998] 1998, 12 (Suppl. 28): Abst P2393); roflumilast (CAS reference No 162401-32-3) and a pthalazinone (WO99/47505, the disclosure of which is hereby incorporated by reference) from Byk-

25 Gulden; Pumafentrine, (-)-p-[(4aR*,10bS*)-9-ethoxy-1,2,3,4,4a,10b-hexahydro-8-methoxy-2-methylbenzo[c][1,6]naphthyridin-6-yl]-N,N-diisopropylbenzamide which is a mixed PDE3/PDE4 inhibitor which has been prepared and published on by Byk-Gulden, now Altana; arofylline under development by Almirall-Prodesfarma; VM554/UM565 from Vernalis; or T-440 (Tanabe Seiyaku; Fuji, K. et al. J Pharmacol Exp Ther, 1998, 284(1):

30 162), and T2585.

Other possible PDE-4 and mixed PDE3/PDE4 inhibitors include those listed in WO01/13953, the disclosure of which is hereby incorporated by reference.

Phosphodiesterase and Rolipram Binding Assays

Assay method 1A

Isolated human monocyte PDE4 and hrPDE (human recombinant PDE4) was determined to exist primarily in the low affinity form. Hence, the activity of test compounds against the low affinity form of PDE4 can be assessed using standard assays for PDE4 catalytic activity employing 1 μ M [3 H]cAMP as a substrate (Torphy *et al.*, J. of Biol. Chem., Vol. 267, No. 3 pp1798-1804, 1992).

Rat brain high speed supernatants were used as a source of protein and both enantiomers of [3 H]-rolipram were prepared to a specific activity of 25.6 Ci/mmol. Standard assay conditions were modified from the published procedure to be identical to the PDE assay conditions, except for the last of the cAMP: 50mM Tris HCl (pH 7.5), 5 mM MgCl₂, 50 μ M 5'-AMP and 1 nM of [3 H]-rolipram (Torphy *et al.*, J. of Biol. Chem., Vol. 267, No. 3 pp1798-1804, 1992). The assay was run for 1 hour at 30° C. The reaction was terminated and bound ligand was separated from free ligand using a Brandel cell harvester. Competition for the high affinity binding site was assessed under conditions that were identical to those used for measuring low affinity PDE activity, expect that [3 H]-cAMP was not present.

Assay method 1B

Measurement of Phosphodiesterase Activity

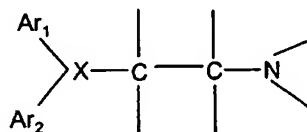
PDE activity was assayed using a [3 H]cAMP SPA or [3 H]cGMP SPA enzyme assay as described by the supplier (Amersham Life Sciences). The reactions were conducted in 96-well plates at room temperature, in 0.1 ml of reaction buffer containing (final concentrations): 50 mM Tris-HCl, pH 7.5, 8.3 mM MgCl₂, 1.7 mM EGTA, [3 H]cAMP or [3 H] cGMP (approximately 2000 dpm/pmol), enzyme and various concentrations of the inhibitors. The assay was allowed to proceed for 1 hr and was terminated by adding 50 μ l of SPA yttrium silicate beads in the presence of zinc sulfate. The plates were shaken and allowed to stand at room temperature for 20 min. Radiolabeled product formation was assessed by scintillation spectrometry.

[3 H]R-rolipram binding assay

- The [³H]R-rolipram binding assay was performed by modification of the method of Schneider and co-workers, see Nicholson, et al., Trends Pharmacol. Sci., Vol. 12, pp.19-27 (1991) and McHale et al., Mol. Pharmacol., Vol. 39, 109-113 (1991). R-Rolipram binds to the catalytic site of PDE4 see Torphy et al., Mol. Pharmacol., Vol. 39, pp. 376-384 (1991). Consequently, competition for [³H]R-rolipram binding provides an independent confirmation of the PDE4 inhibitor potencies of unlabeled competitors. The assay was performed at 30°C for 1 hr in 0.5 µl buffer containing (final concentrations): 50 mM Tris-HCl, pH 7.5, 5 mM MgCl₂, 0.05% bovine serum albumin, 2 nM [³H]R-rolipram (5.7 x 10⁴ dpm/pmol) and various concentrations of non-radiolabeled inhibitors.
- The reaction was stopped by the addition of 2.5 ml of ice-cold reaction buffer (without [³H]-R-rolipram) and rapid vacuum filtration (Brandel Cell Harvester) through Whatman GF/B filters that had been soaked in 0.3% polyethylenimine. The filters were washed with an additional 7.5 ml of cold buffer, dried, and counted via liquid scintillation spectrometry.
- Suitable anticholinergic agents are those compounds that act as antagonists at the muscarinic receptor, in particular those compounds which are antagonists of the M₁ and M₂ receptors. Exemplary compounds include the alkaloids of the belladonna plants as illustrated by the likes of atropine, scopolamine, homatropine, hyoscyamine; these compounds are normally administered as a salt, being tertiary amines. These drugs, particularly the salt forms, are readily available from a number of commercial sources or can be made or prepared from literature data via, to wit:
- Atropine - CAS-51-55-8 or CAS-51-48-1 (anhydrous form), atropine sulfate - CAS-5908-99-6; atropine oxide - CAS-4438-22-6 or its HCl salt - CAS-4574-60-1 and methylatropine nitrate - CAS-52-88-0.
- Homatropine - CAS-87-00-3, hydrobromide salt - CAS-51-56-9, methylbromide salt - CAS-80-49-9.
- Hyoscyamine (*d, l*) - CAS-101-31-5, hydrobromide salt - CAS-306-03-6 and sulfate salt - CAS-6835-16-1.
- Scopolamine - CAS-51-34-3, hydrobromide salt - CAS-6533-68-2, methylbromide salt - CAS-155-41-9.
- Preferred anticholinergics include ipratropium (e.g. as the bromide), sold under the name Atrovent, oxitropium (e.g. as the bromide) and tiotropium (e.g. as the bromide)

(CAS-139404-48-1). Also of interest are: methantheline (CAS-53-46-3), propantheline bromide (CAS- 50-34-9), anisotropine methyl bromide or Valpin 50 (CAS- 80-50-2), clidinium bromide (Quarzan, CAS-3485-62-9), copyrolate (Robinul), isopropamide iodide (CAS-71-81-8), mepenzolate bromide (U.S. patent 2,918,408), tridihexethyl chloride (Pathilone, CAS-4310-35-4), and hexocyclium methylsulfate (Tral, CAS-115-63-9). See also cyclopentolate hydrochloride (CAS-5870-29-1), tropicamide (CAS-1508-75-4), trihexyphenidyl hydrochloride (CAS-144-11-6), pirenzepine (CAS-29868-97-1), telenzepine (CAS-80880-90-9), AF-DX 116, or methoctramine, and the compounds disclosed in WO01/04118, the disclosure of which is hereby incorporated by reference.

Suitable antihistamines (also referred to as H₁-receptor antagonists) include any one or more of the numerous antagonists known which inhibit H₁-receptors, and are safe for human use. All are reversible, competitive inhibitors of the interaction of histamine with H₁-receptors. The majority of these inhibitors, mostly first generation antagonists, have a core structure, which can be represented by the following formula:



This generalized structure represents three types of antihistamines generally available: ethanolamines, ethylenediamines, and alkylamines. In addition, other first generation antihistamines include those which can be characterized as based on piperazine and phenothiazines. Second generation antagonists, which are non-sedating, have a similar structure-activity relationship in that they retain the core ethylene group (the alkylamines) or mimic the tertiary amine group with piperazine or piperidine. Exemplary antagonists are as follows:

Ethanolamines: carbinoxamine maleate, clemastine fumarate, diphenylhydramine hydrochloride, and dimenhydrinate.

Ethylenediamines: pyrilamine amleate, tripeleennamine HCl, and tripeleennamine citrate.

Alkylamines: chlorpheniramine and its salts such as the maleate salt, and acrivastine.

Piperazines: hydroxyzine HCl, hydroxyzine pamoate, cyclizine HCl, cyclizine lactate, meclizine HCl, and cetirizine HCl.

Piperidines: Astemizole, levocabastine HCl, loratadine or its descarboethoxy analogue, and terfenadine and fexofenadine hydrochloride or another pharmaceutically acceptable salt.

Azelastine hydrochloride is yet another H₁ receptor antagonist which may be used in combination with a PDE4 inhibitor.

Examples of preferred anti-histamines include methapyrilene and loratadine.

10 The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a PDE4 inhibitor.

15 The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a corticosteroid.

20 The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an anticholinergic.

25 The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an antihistamine.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a PDE4 inhibitor and a corticosteroid.

30 The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an anticholinergic and a PDE-4 inhibitor.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a physiologically acceptable diluent or carrier represent a further aspect of the invention.

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The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

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Hereinafter, the term "active ingredient" means a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

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The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), inhalation (including fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulisers or insufflators), rectal and topical (including dermal, buccal, sublingual and intraocular) administration, although the most suitable route may depend upon, for example, the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

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Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

5 A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

10 Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose
15 containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example saline or water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets
20 of the kind previously described.

Dry powder compositions for topical delivery to the lung by inhalation may, for example, be presented in capsules and cartridges of for example gelatine, or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator. Formulations
25 generally contain a powder mix for inhalation of the compound of the invention and a suitable powder base (carrier substance) such as lactose or starch. Use of lactose is preferred. Each capsule or cartridge may generally contain between 20µg-10mg of the compound of formula (I) optionally in combination with another therapeutically active ingredient. Alternatively, the compound of the invention may be presented without
30 excipients. Packaging of the formulation may be suitable for unit dose or multi-dose delivery. In the case of multi-dose delivery, the formulation can be pre-metered (eg as in Diskus, see GB 2242134 or Diskhaler, see GB 2178965, 2129691 and 2169265) or metered in use (eg as in Turbuhaler, see EP 69715). An example of a unit-dose device is Rotahaler (see GB 2064336). The Diskus inhalation device comprises an elongate

strip formed from a base sheet having a plurality of recesses spaced along its length and a lid sheet hermetically but peelably sealed thereto to define a plurality of containers, each container having therein an inhalable formulation containing a compound of formula (I) preferably combined with lactose. Preferably, the strip is sufficiently flexible to be wound into a roll. The lid sheet and base sheet will preferably have leading end portions which are not sealed to one another and at least one of the said leading end portions is constructed to be attached to a winding means. Also, preferably the hermetic seal between the base and lid sheets extends over their whole width. The lid sheet may preferably be peeled from the base sheet in a longitudinal direction from a first end of the said base sheet.

Spray compositions for topical delivery to the lung by inhalation may for example be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as a metered dose inhaler, with the use of a suitable liquefied propellant. Aerosol compositions suitable for inhalation can be either a suspension or a solution and generally contain the compound of formula (I) optionally in combination with another therapeutically active ingredient and a suitable propellant such as a fluorocarbon or hydrogen-containing chlorofluorocarbon or mixtures thereof, particularly hydrofluoroalkanes, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, especially 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or a mixture thereof. Carbon dioxide or other suitable gas may also be used as propellant. The aerosol composition may be excipient free or may optionally contain additional formulation excipients well known in the art such as surfactants eg oleic acid or lecithin and cosolvents eg ethanol. Pressurised formulations will generally be retained in a canister (eg an aluminium canister) closed with a valve (eg a metering valve) and fitted into an actuator provided with a mouthpiece.

Medicaments for administration by inhalation desirably have a controlled particle size. The optimum particle size for inhalation into the bronchial system is usually 1-10 μ m, preferably 2-5 μ m. Particles having a size above 20 μ m are generally too large when inhaled to reach the small airways. To achieve these particle sizes the particles of the active ingredient as produced may be size reduced by conventional means eg by micronisation. The desired fraction may be separated out by air classification or sieving.

Preferably, the particles will be crystalline. When an excipient such as lactose is employed, generally, the particle size of the excipient will be much greater than the inhaled medicament within the present invention. When the excipient is lactose it will typically be present as milled lactose, wherein not more than 85% of lactose particles will have a MMD of 60-90 μ m and not less than 15% will have a MMD of less than 15 μ m.

Intranasal sprays may be formulated with aqueous or non-aqueous vehicles with the addition of agents such as thickening agents, buffer salts or acid or alkali to adjust the pH, isotonicity adjusting agents or anti-oxidants.

Solutions for inhalation by nebulisation may be formulated with an aqueous vehicle with the addition of agents such as acid or alkali, buffer salts, isotonicity adjusting agents or antimicrobials. They may be sterilised by filtration or heating in an autoclave, or presented as a non-sterile product.

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter or polyethylene glycol.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

Preferred unit dosage formulations are those containing an effective dose, as hereinbefore recited, or an appropriate fraction thereof, of the active ingredient.

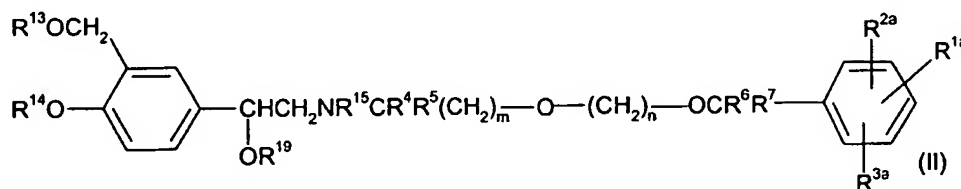
It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

According to a further aspect of the invention, there is provided a process for preparing a compound of formula (I) or (Ia) or a salt, solvate, or physiologically functional

derivative thereof which comprises a process as described below followed where necessary or desired by one or more of the following steps in any order:

- (i) optional removal of any protecting groups;
- (ii) optional separation of an enantiomer or diastereoisomer from a mixture of enantiomers or diastereoisomers;
- (iii) optional conversion of the product to a corresponding salt, solvate, or physiologically functional derivative thereof.
- (iv) optional conversion of a group R^{1a} , R^{2a} and/or R^{3a} to a group R^1 , R^2 and/or R^3 respectively.

In one general process (A), a compound of formula (I) or (Ia) may be obtained by deprotection of a protected intermediate, for example of formula (II):



or a salt or solvate thereof, wherein R^4 , R^5 , R^6 , R^7 , m , and n are as defined for the compound of formula (I) or (Ia), and R^{1a} , R^{2a} , and R^{3a} are each independently either the same as R^1 , R^2 , and R^3 respectively as defined for the compound of formulae (I) or (Ia) or a precursor for said group R^1 , R^2 , or R^3 , and R^{13} , R^{14} , and R^{15} are each independently either hydrogen or a protecting group provided that at least one of R^{13} , R^{14} , and R^{15} is a protecting group, and R^{19} is hydrogen or a protecting group.

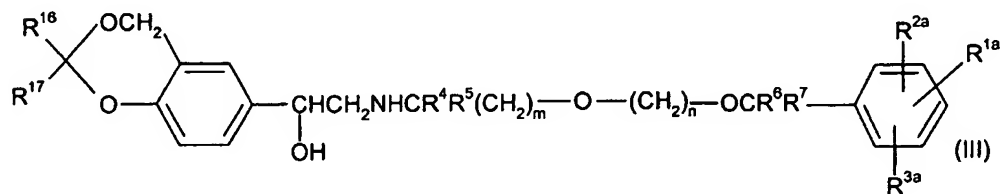
Suitable protecting groups may be any conventional protecting group such as those described in "Protective Groups in Organic Synthesis" by Theodora W Greene and Peter G M Wuts, 3rd edition (John Wiley & Sons, 1999). Examples of suitable hydroxyl protecting groups represented by R^{13} and R^{14} are esters such as acetate ester, aralkyl groups such as benzyl, diphenylmethyl, or triphenylmethyl, and tetrahydropyranyl. Examples of suitable amino protecting groups represented by R^{15} include benzyl, α -

methylbenzyl, diphenylmethyl, triphenylmethyl, benzyloxycarbonyl, tert-butoxycarbonyl, and acyl groups such as trichloroacetyl or trifluoroacetyl.

As will be appreciated by the person skilled in the art, use of such protecting groups may include orthogonal protection of groups in the compounds of formula (II) to facilitate the selective removal of one group in the presence of another, thus enabling selective functionalisation of a single amino or hydroxyl function. For example, the $-\text{CH}(\text{OH})$ group may be orthogonally protected as CHOR^{19} using, for example, a trialkylsilyl group such as triethylsilyl. A person skilled in the art will also appreciate other orthogonal protection strategies, available by conventional means as described in Theodora W Greene (see above).

The deprotection to yield a compound of formula (I) or (Ia) may be effected using conventional techniques. It will be apparent to persons skilled in the art that the deprotection method employed should not effect cleavage of the $-\text{OCR}^6\text{R}^7$ moiety.

When R^{13} and/or R^{14} is tetrahydropyranyl this may be cleaved by hydrolysis under acidic conditions, for example using aqueous acetic acid. Acyl groups represented by R^{15} may be removed by hydrolysis, for example with a base such as sodium hydroxide, or a group such as trichloroethoxycarbonyl may be removed by reduction with, for example, zinc and acetic acid. Other deprotection methods may be found in Theodora W Greene (see above). In a particular embodiment of the above process, R^{13} and R^{14} may together represent a protecting group as in the compound of formula (III):



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or a salt or solvate thereof, wherein R^4 , R^5 , R^6 , R^7 , m , and n are as defined for the compound of formula (I) or (Ia), and R^{1a} , R^{2a} , and R^{3a} are each independently either the same as R^1 , R^2 , and R^3 respectively as defined for the compound of formulae (I) or (Ia) or a precursor for said group R^1 , R^2 , or R^3 .

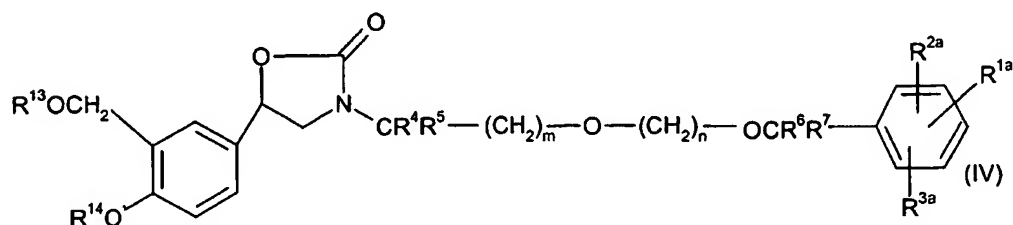
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R^{16} and R^{17} are independently selected from hydrogen, C_{1-6} alkyl, or aryl. In a preferred aspect, both R^{16} and R^{17} are methyl.

A suitable precursor group R^{1a} , R^{2a} , and/or R^{3a} in the compounds of formulae (II) and (III) would be a group which is convertible to the desired group R^1 , R^2 , and/or R^3 , before, after or simultaneously with the removal of the protecting groups R^{13} , R^{14} , and/or R^{15} . For example, R^{1a} , R^{2a} , and/or R^{3a} may suitably be a protected version of a group R^1 , R^2 , and R^3 respectively, such that removal of the protecting group gives the desired group R^1 , R^2 , or R^3 . Preferred protecting groups in R^{1a} , R^{2a} , and/or R^{3a} are those which may be removed under the conditions used for the removal of the protecting groups R^{13} , R^{14} , and/or R^{15} .

The compound of formula (III) may be converted to a compound of formula (I) or (Ia) by hydrolysis with dilute aqueous acid, for example acetic acid or hydrochloric acid in a suitable solvent or by transketalisation in an alcohol, for example ethanol, in the presence of a catalyst such as an acid (for example, toluenesulphonic acid) or a salt (such as pyridinium tosylate) at normal or elevated temperature.

Compounds of formulae (II) and (III) wherein R^{15} is hydrogen may be prepared from the corresponding compound of formula (IV):



or a salt or solvate thereof, wherein R^4 , R^5 , R^6 , R^7 , R^{13} , R^{14} , m , and n are as defined for the compound of formula (II) or (III) and R^{1a} , R^{2a} , and R^{3a} are each independently either the same as R^1 , R^2 , and R^3 respectively as defined for the compound of formula (II) or (III) or a precursor for said group R^1 , R^2 , or R^3 .

A suitable precursor group R^{1a} , R^{2a} , and/or R^{3a} in the compound of formula (IV) would be a group which is convertible to the desired group R^1 , R^2 , and/or R^3 . Suitably, such

conversions are carried out using conventional methods which are known in the art. For example, where R^1 is to be $-NR^8SO_2R^9$, a suitable precursor group R^{1a} in the compound of formula (IV) would have the amine $-NHR^8$ in place of the substituent R^1 , such that the desired substituent R^1 may be formed by reaction with the appropriate sulphonyl chloride (i.e. R^9SO_2Cl) before deprotection to form the compound of formula (I).

As a second example, where R^1 is to be $-NR^8C(O)NHR^9$, a suitable precursor group R^{1a} in the compound of formula (IV) would have the amine $-NHR^8$ in place of the substituent R^1 , such that the desired substituent R^1 may be formed by reaction with the appropriate isocyanate (i.e. R^9NCO) before deprotection to form the compound of formula (I).

Alternatively, where R^1 is to be $-NHC(O)NHR^9$, a suitable precursor group R^{1a} in the compound of formula (IV) has $-NO_2$ in place of the substituent R^1 which may be reduced to form the corresponding primary amine before reaction with the isocyanate R^9NCO as described above to form the desired urea substituent R^1 . The reduction of the $-NO_2$ group may be effected by any suitable method such as hydrogenation in the presence of a catalyst, for example, palladium/charcoal or platinum oxide, or by reaction with aluminium amalgam in tetrahydrofuran, or with zinc in ammonium chloride solution.

As a further example, where R^1 is to be $-NR^8C(O)R^9$, a suitable precursor group R^{1a} in the compound of formula (IV) would have the amine $-NHR^8$ in place of the substituent R^1 , such that the desired substituent R^1 may be formed by reaction with the appropriate acyl chloride (i.e. $R^9C(O)Cl$) before deprotection to form the compound of formula (I).

As a further example, where R^1 is to be $-NR^8C(O)OR^9$, a suitable precursor group R^{1a} in the compound of formula (IV) would have the amine $-NHR^8$ in place of the substituent R^1 , such that the desired substituent R^1 may be formed by reaction with the appropriate chloroformate (i.e. $R^9OC(O)Cl$) before deprotection to form the compound of formula (I).

Alternatively, where R^1 is to be an optionally substituted aryl group, a suitable precursor group R^{1a} in the compound of formula (IV) would have a halo substituent, for example iodo, in place of the substituent R^1 , such that the desired substituent R^1 may be formed by reaction with bis(pinacolato)diboron followed by reaction with the appropriate optionally substituted haloaryl group, before deprotection to form the compound of formula (I). Alternatively, where R^1 is to be an optionally substituted aryl group, a suitable precursor group R^{1a} in the compound of formula (IV) would have a halo

substituent, for example iodo, in place of the substituent R^1 , such that the desired substituent R^1 may be formed by reaction with the appropriate optionally substituted arylboronic acid, for example an optionally substituted phenylboronic acid, before deprotection to form the compound of formula (I).

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Alternatively, R^{1a} , R^{2a} , and/or R^{3a} may suitably be a protected version of a group R^1 , R^2 , and R^3 respectively, such that removal of the protecting group gives the desired group R^1 , R^2 , or R^3 . Preferred protecting groups in R^{1a} , R^{2a} , and/or R^{3a} are those which may be removed under the conditions used for the removal of the protecting groups R^{13} and R^{14} , or the conditions used for the conversion of the compound of formula (IV) to the compound of formulae (II) or (III). For example, an $-NH-$ group in the desired group R^1 , R^2 , or R^3 may be protected by a 2-(trimethylsilyl)ethoxymethyl group or a tert-butoxycarbonyl group.

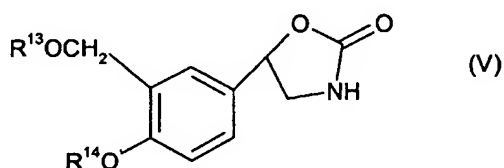
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The conversion of a compound of formula (IV) to a compound of formula (II) or (III) may be effected by treatment with a base, for example a non-aqueous base, such as potassium trimethylsilanolate, or an aqueous base such as aqueous sodium hydroxide, in a suitable solvent such as tetrahydrofuran.

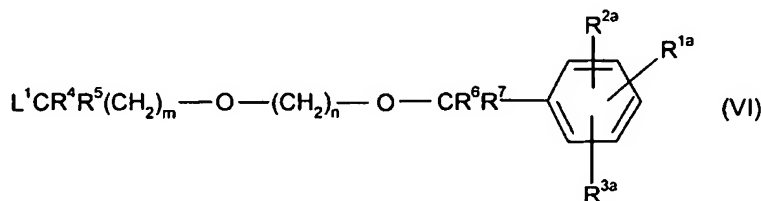
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Compounds of formula (IV) may be prepared according to a first method (a) by coupling the corresponding compound of formula (V):



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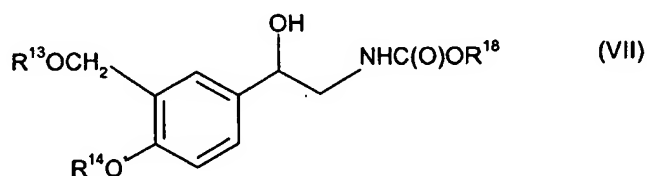
or a salt or solvate thereof, wherein R^{13} and R^{14} are as defined for the compound of formula (IV) with a compound of formula (VI):



wherein R^{1a} , R^{2a} , R^{3a} , R^4 , R^5 , R^6 , R^7 , m , and n are as defined for the compound of formula (IV) and L^1 is a leaving group, for example a halo group (typically bromo or iodo) or a sulphonate such as an alkyl sulphonate (typically, methanesulphonate), an arylsulphonate (typically, toluenesulphonate), or a haloalkyl sulphonate (typically, trifluoromethanesulphonate).

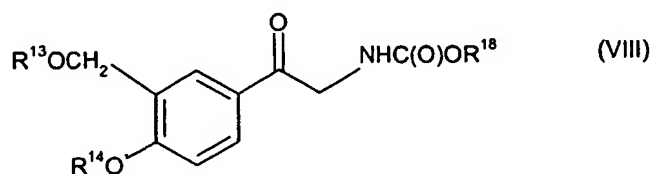
The coupling of a compound of formula (V) with a compound of formula (VI) may be effected in the presence of a base, such as a metal hydride, for example sodium hydride, an anhydride such as potassium t-butoxide or an inorganic base such as caesium carbonate, in an aprotic solvent, for example dimethylformamide.

Compounds of formula (V) may be prepared by ring closure of a compound of formula (VII):



wherein R^{13} and R^{14} are as defined for the compound of formula (V) and R^{18} is C_{1-6} alkyl, for example tert-butyl, or aryl, for example phenyl. The ring closure may be effected by treatment with a base, such as a metal hydride, for example sodium hydride, in the presence of an aprotic solvent, for example, dimethylformamide.

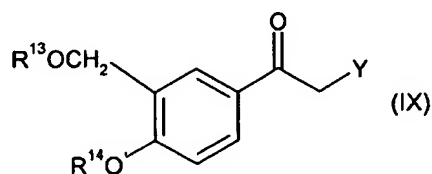
Compounds of formula (VII) may be prepared from the corresponding ketone of formula (VIII):



wherein R^{13} , R^{14} and R^{18} are as defined for the compound of formula (VII), by reduction by any suitable method, for example by treatment with borane, in the presence of a

chiral catalyst, such as CBS-oxazaborolidine, in a suitable solvent such as tetrahydrofuran.

The compound of formula (VIII) may be prepared from the corresponding halide of formula (IX):

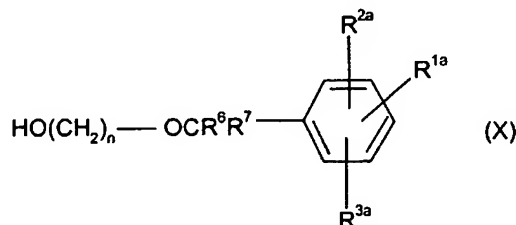


wherein R^{13} and R^{14} are as defined for the compound of formula (VIII) and Y is a halo group, suitably bromo.

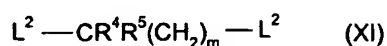
The conversion of a compound of formula (IX) to a compound of formula (VIII) may be effected by reaction with the protected amine $\text{HN}(\text{COOR}^{18})_2$ wherein R^{18} is as defined for the compound of formula (VIII) in the presence of an inorganic base such as caesium carbonate, followed by selective removal of one of the COOR^{18} groups, for example by treatment with an acid such as trifluoroacetic acid.

Compounds of formula (IX) may be prepared from the corresponding compound having free hydroxymethyl and hydroxy substituents by forming the protected groups $R^{13}\text{OCH}_2$ - and $R^{14}\text{O}$ - wherein R^{13} and R^{14} are as defined for the compound of formula (IX). Such methods are described in DE 3513885 (Glaxo).

Compounds of formula (VI) may be prepared by coupling a compound of formula (X):



wherein R^{1a} , R^{2a} , R^{3a} , R^6 , R^7 , and n are as defined for the compound of formula (VI), with a compound of formula (XI):



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wherein R^4 , R^5 , and m are as defined for the compound of formula (VI), and L^2 is a leaving group such as halo (typically bromo).

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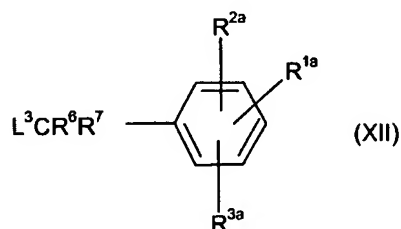
The coupling of compounds (X) and (XI) may be effected in the presence of a base, such as a metal hydride, for example sodium hydride, or an inorganic base such as caesium carbonate, in an aprotic solvent, for example dimethylformamide. Alternatively, the coupling of compounds (X) and (XI) may be effected under phase transfer conditions, suitably in excess aqueous alkali such as 50% aqueous sodium hydroxide, optionally in the presence of a phase transfer catalyst such as a tetrabutylammonium salt, for example tetrabutylammonium bromide.

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Compounds of formula (XI) are commercially available or may be prepared by methods well known to the person skilled in the art.

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Compounds of formula (X) may be prepared by coupling the corresponding compound of formula (XII):



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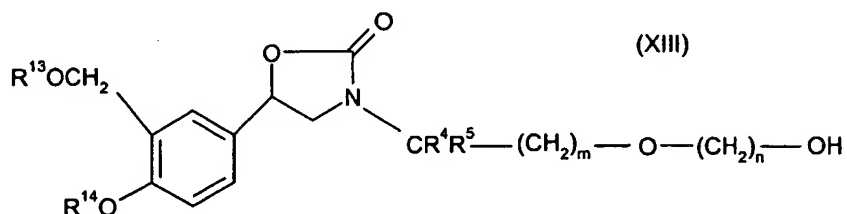
wherein R^{1a} , R^{2a} , R^{3a} , R^6 , and R^7 are as defined for the desired compound of formula (X), and L^3 is a leaving group such as halo (typically bromo);

with the dihydroxy compound of formula $HO(CH_2)_nOH$ wherein n is as defined for the compound of formula (X). The coupling of a compound of formula (XII) with the

dihydroxy compound may be effected by methods analogous to those described for the coupling of compounds (X) and (XI).

Compounds of formula (XII) are commercially available or may be prepared by methods well known to the person skilled in the art.

According to an alternative process (b), a compound of formula (IV) as defined above may be prepared by coupling the corresponding compound of formula (XIII):



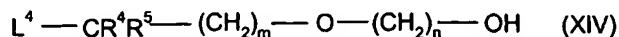
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wherein R^4 , R^5 , R^{13} , R^{14} , m , and n are as defined for the desired compound of formula (IV), with the corresponding compound of formula (XII) as defined above in which R^{1a} , R^{2a} , R^{3a} , R^6 , and R^7 are as defined for the desired compound of formula (IV) and L^3 is a leaving group such as halo (typically bromo). This coupling may be effected by methods analogous to those described for the coupling of compounds (X) and (XI).

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Compounds of formula (XIII) may be prepared by coupling the corresponding compound of formula (V) as defined above wherein R^{13} and R^{14} are as defined for the desired compound of formula (XIII) with the corresponding compound of formula (XIV):

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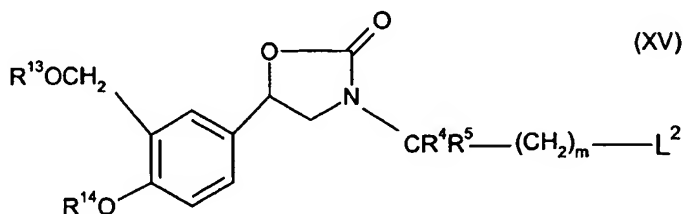
or a protected derivative thereof, wherein R^4 , R^5 , m and n are as defined for the desired compound of formula (XIII) and L^4 is a leaving group such as halo (typically bromo). The coupling of compounds of formulae (V) and (XIV) may be effected by methods analogous to those described for the coupling of compounds of formulae (X) and (XI).

30

Compounds of formula (XIV) may be prepared from the corresponding compounds of formula (XI) as defined above with the dihydroxy compound of formula $\text{HO}(\text{CH}_2)_n\text{OH}$

wherein n is as defined for the desired compound of formula (XIV), by methods analogous to those described for the coupling of compounds of formula (X) and (XI).

- 5 Alternatively, compounds of formula (XIII) may be prepared by coupling the corresponding compound of formula (XV):



- 10 wherein R^{13} , R^{14} , R^4 , R^5 , and m are as defined for the desired compound of formula (XIII) and L^2 is a leaving group such as halo (typically bromo), followed by coupling the compound of formula (XV) with the dihydroxy compound of formula $HO(CH_2)_nOH$, wherein n is as defined for the desired compound of formula (XIII), by methods analogous to those described for the coupling of compounds of formula (X) and (XI).

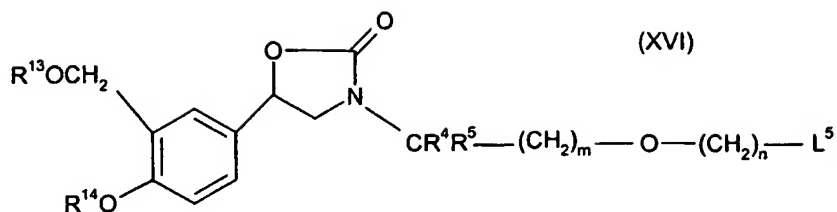
- 15 The compound of formula (XV) may be prepared by coupling the corresponding compound of formula (V) as previously defined wherein R^{13} and R^{14} are as defined for the desired compound of formula (XIII), with the corresponding compound of formula (XI) as previously defined wherein R^4 , R^5 , and m are as defined for the desired compound of formula (XIII) and L^2 is a leaving group such as halo (typically bromo).

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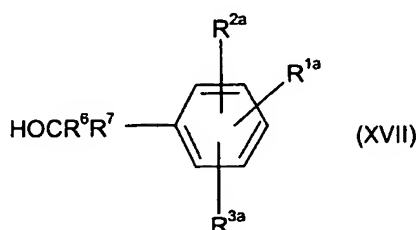
The coupling of compounds of formulae (V) and (XI) may be effected by methods analogous to those described for the coupling of compounds of formulae (V) and (VI).

- 25 In a further alternative process (c) compounds of formula (IV) as defined above may be prepared by coupling the corresponding compound of formula (XVI):

38



5 wherein R^{13} , R^{14} , R^4 , R^5 , m and n are as defined for the compound of formula (IV) and L^5 is a leaving group, for example a sulphonate such as an alkyl sulphonate (typically, methanesulphonate), an arylsulphonate (typically, toluenesulphonate), or a haloalkyl sulphonate (typically, trifluoromethanesulphonate), with a compound of formula (XVII):



10

wherein R^{1a} , R^{2a} , R^{3a} , R^6 , and R^7 are as defined for the compound of formula (IV).

The coupling of compounds of formulae (XVI) and (XVII) may be effected by methods analogous to those described for the coupling of compounds of formulae (V) and (VI).

15

The compound of formula (XVI) may be prepared by converting the hydroxyl group in a compound of formula (XIII) into a leaving group L^4 such as a methanesulphonate group using methods known in the art, for example by reaction with methanesulphonyl chloride in the presence of a suitable base, for example $NEt(iPr)_2$, in a suitable solvent such as dichloromethane.

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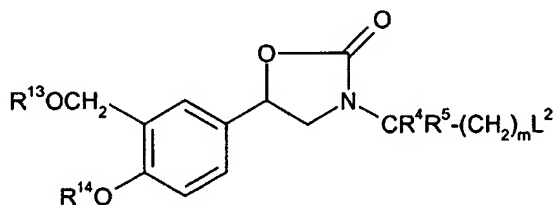
The compounds of formula (XVII) are commercially available or may be prepared using methods known in the art.

25

During the synthesis of the compound of formula (XIII), appropriate protecting chemistry may be used, for example, the compounds of formula (XIV) and the dihydroxy

compound of formula $\text{HO}(\text{CH}_2)_n\text{OH}$ may be protected so as to improve the yield of the desired intermediates. Suitable protecting strategies will be appreciated by the person skilled in the art and may also be found in Theodora W. Greene (see above). Thus, for example, a primary hydroxyl group may be protected with a trialkylsilyl group such as tert-butyldimethylsilyl or with a benzyl group.

In a further process (d) compounds of formula (IV) as defined above may be prepared by coupling a compound of formula (XVIII):



(XVIII)

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wherein R^{13} , R^{14} , R^4 , R^5 , and m are as defined for formula (IV) and L^2 is defined as for formula (XI),

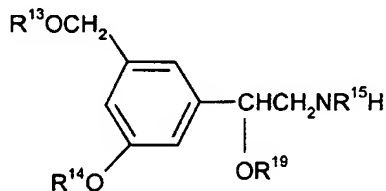
with a compound of formula (X) as defined above. The reaction of compounds (XVIII) and (X) may be effected in a similar manner to the coupling of compounds (XI) and (X).

15

Compounds of formula (XVIII) may be prepared by reacting a compound of formula (V) with a compound of formula (XI) in a similar manner to the reaction of compounds (V) and (XIV).

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In a further general process (B) a compound of formula (I) and (Ia) may be obtained by alkylation of an amine of formula (XIX):



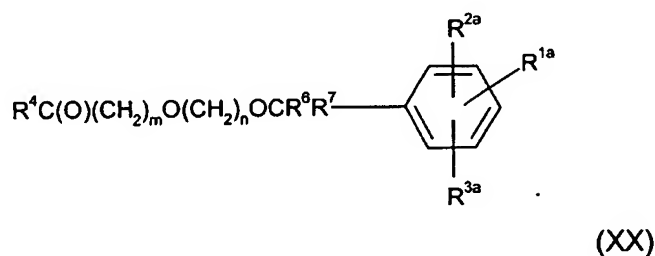
(XIX)

wherein R^{13} , R^{14} , R^{15} and R^{19} are as hereinbefore defined,
 with a compound of formula (VI) wherein L^1 represents a leaving group such as halo
 (typically bromo), followed by removal of any protecting groups present by conventional
 methods as described above for the deprotection of compounds of formula (II).

The reaction of compounds of formulae (XIX) and (VI) may be optionally effected in the
 presence of an organic base, such as a trialkylamine, for example diisopropyl
 ethylamine, and in a suitable solvent, for example dimethylformamide.

Compounds of formula (XIX) are known in the art, for example EP-A-0947498, or may
 readily be prepared by a person skilled in the art.

In a yet further general process (C), a compound of formula (I) or (Ia) may be prepared
 by reacting an amine of formula (XIX) as defined hereinabove, with a compound of
 formula (XX):



wherein R^4 , R^6 , R^7 , R^{1a} , R^{2a} , R^{3a} , m and n are as hereinbefore defined;
 under conditions suitable to effect reductive amination, for example in the presence of a
 reducing agent such as borohydride, typically tetramethylammonium (triacetoxo)
 borohydride.

A compound of formula (XX) may be prepared by methods known in the art, for
 example from a compound of formula (VI) as defined hereinabove via Kornblum
 oxidation.

It will be appreciated that in any of the general processes (A), (B) or (C) as well as the
 processes for (a) to (d) for preparing compounds (IV) described above, the precise

order of the synthetic steps by which the various groups and moieties are introduced into the molecule may be varied. It will be within the skill of the practitioner in the art to ensure that groups or moieties introduced at one stage of the process will not be affected by subsequent transformations and reactions, and to select the order of synthetic steps accordingly. It will also be appreciated that in general processes (B) and (C) appropriate protecting groups may be employed if necessary and/or desired and removed at any suitable stage of the synthesis, eg. in the last stage, as described in general process (A).

The enantiomeric compounds of the invention may be obtained (i) by separation of the components of the corresponding racemic mixture, for example, by means of a chiral chromatography column, enzymic resolution methods, or preparing and separating suitable diastereoisomers, or (ii) by direct synthesis from the appropriate chiral intermediates by the methods described herein.

Optional conversion of a compound of formula (I) or (Ia) to a corresponding salt may conveniently be effected by reaction with the appropriate acid or base. Optional conversion of a compound of formula (I) or (Ia) to a corresponding solvate or physiologically functional derivative may be effected by methods known to those skilled in the art.

According to a further aspect, the present invention provides novel intermediates for the preparation of compounds of formula (I) or (Ia), for example:

compounds of formula (II) and (III) as defined above, or an optical isomer, a salt, or a protected derivative thereof; particularly, a compound selected from:

N-[3-({2-[(6-[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]ethoxy)methyl)phenyl]-N'-phenylurea; and
 (1R)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol;
 N-cyclohexyl-N-[3-({2-[(6-[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]ethoxy)methyl)phenyl]urea;
 N-(1,1'-biphenyl-4-yl)-N'-[3-({2-[(6-[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]ethoxy)methyl)phenyl]urea;
 N-cyclopropyl-3'-[2-[(6-[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]ethoxy)methyl]-1,1'-biphenyl-2-sulfonamide;

- (1R)-2-[[6-(2-[[3-(2,3-dihydroimidazo[2,1-b][1,3]thiazol-6-ylmethyl)amino]-phenyl)methoxy]ethoxy)hexyl]amino]-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol;
 N-{3-[[2-[[6-[[[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]-amino]hexyl]oxy]ethoxy)methyl]phenyl]-3-[(phenylsulfonyl)amino]benzamide;
 5 N-(3-[[[3-[[2-[[6-[[[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino]hexyl]oxy]ethoxy)methyl]phenyl]amino)carbonyl]amino]phenyl)-pyridine-3-carboxamide;
 N-cyclohexyl-3-[[2-[[6-[[[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino]hexyl]oxy]ethoxy)methyl]-N-([2-(trimethylsilyl)ethyl]-oxy)methyl]benzenesulfonamide;
 10 3'-[[2-[[6-[[[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]-amino]hexyl]oxy]ethoxy)methyl]-1,1'-biphenyl-3-ol;
 (1R)-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-[[6-(2-[(3-iodobenzyl)oxy]-ethoxy)hexyl]amino]ethanol;
 15 N-{3-[[2-[[6-[[[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]-amino]hexyl]oxy]ethoxy)methyl]phenyl]-N'-[3-(phenylethynyl)phenyl]urea;
 (1R)-2-[[6-(2-[[3'-[2,4-bis[(1,1-dimethylethyl)oxy]pyrimidin-5-yl]-1,1'-biphenyl-3-yl]methoxy]ethoxy)hexyl]amino]-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol; and
 cyclopentyl 3-[[2-[[6-[[[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino]hexyl]oxy]ethoxy)methyl]phenyl]carbamate;
 20 and other similar intermediates exemplified hereinafter;
- compounds of formula (IV) as defined above, or an optical isomer, a salt, or a protected derivative thereof; particularly, a compound selected from:
- 25 (5R)-3-(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one;
 (5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-3-(6-{2-[(3-nitrobenzyl)oxy]-ethoxy}hexyl)-1,3-oxazolidin-2-one;
 N-(3-[[2-[[6-[(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl]oxy]ethoxy)methyl]phenyl)-N'-phenylurea;
 30 N-cyclohexyl-N'-(3-[[2-[[6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl]oxy]ethoxy)methyl]phenyl)urea;
 N-(1,1'-biphenyl-4-yl)-N'-(3-[[2-[[6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl]oxy]ethoxy)methyl]phenyl)urea;

- (5R)-3-(6-{2-[(3-aminobenzyl)oxy]ethoxy}hexyl)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one;
- (5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-3-{6-[2-[(3-nitrophenyl)methyl]oxy]ethoxy}hexyl)-1,3-oxazolidin-2-one;
- 5 N-[3-({2-({6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)ethoxy)methyl}phenyl]-3-[(phenylsulfonyl)amino]-benzamide;
- 3-amino-N-[3-({2-({6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)ethoxy)methyl}phenyl]benzamide;
- N-[3-({2-({6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)ethoxy)methyl}phenyl]-3-nitrobenzamide;
- 10 N-(3-aminophenyl)-N'-[3-({2-({6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)ethoxy)methyl}phenyl]urea;
- N-[3-({2-({6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)ethoxy)methyl}phenyl]-N'-(3-nitrophenyl)urea;
- 15 N-cyclohexyl-3-({2-({6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)ethoxy)methyl)-N-({2-(trimethylsilyl)ethyl}oxy)-methyl)benzenesulfonamide;
- N-[3-({3-({2-({6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)ethoxy)methyl}phenyl)amino)carbonyl)amino]-phenyl]pyridine-3-
- 20 carboxamide;
- cyclopentyl 3-({2-({6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)ethoxy)methyl}phenyl)carbamate;
- N-[3-({2-({6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)ethoxy)methyl}phenyl]-N'-[3-(phenylethynyl)phenyl]urea;
- 25 1,1-dimethylethyl cyclopropyl{[3'-({2-({6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)ethoxy)methyl)-1,1'-biphenyl-2-yl]sulfonyl}carbamate;
- (5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-3-(6-{2-[(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methoxy)ethoxy}hexyl)-1,3-oxazolidin-2-one;
- 30 (5R)-3-[6-[2-[(3-[(2,3-dihydroimidazo[2,1-b][1,3]thiazol-6-ylmethyl)amino]-phenyl]methoxy]ethoxy]hexyl)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one;
- (5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-3-{6-[2-[(3-iodophenyl)methoxy]ethoxy]hexyl)-1,3-oxazolidin-2-one;

(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-3-[6-[2-[(3'-hydroxy-1,1'-biphenyl-3-yl)methoxy]ethoxy]hexyl]-1,3-oxazolidin-2-one; and

(5R)-3-[6-[2-[(3'-[2,4-bis[(1,1-dimethylethyl)oxy]pyrimidin-5-yl)-1,1'-biphenyl-3-yl)methoxy]ethoxy]hexyl]-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-

5 one;

and other similar intermediates exemplified hereinafter;

compounds of formula (XIII) as defined above, or an optical isomer, a salt, or a protected derivative thereof; particularly, the compound:

10 (5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-3-[6-(2-hydroxyethoxy)hexyl]-1,3-oxazolidin-2-one,

and other similar intermediates exemplified hereinafter.

For a better understanding of the invention, the following Examples are given by way of
15 illustration.

SYNTHETIC EXAMPLES

Throughout the examples, the following abbreviations are used:

20 LCMS: Liquid Chromatography Mass Spectrometry

MS: mass spectrum

TSP +ve: thermospray mass spectrum positive mode

SPE: solid phase extraction

XRPD -x-ray powder diffraction

25 RT: retention time

THF : tetrahydrofuran

DMF : N,N-dimethylformamide

EtOAc: ethyl acetate

EtOH: ethanol

30 MeOH: methanol

MIBK: methyl-isobutylketone

PE: petroleum ether 40°-60°

HPLC: high performance liquid chromatography

TLC: thin layer chromatography

35 Sat: saturated

- bp: boiling point
ca : circa
h: hour(s)
min: minute(s)
- 5 d: doublet
dd: double doublet
s: singlet
brs: broad singlet
- 10 All temperatures are given in degrees centigrade.
- Ammonia refers to 0.880 (aqueous) ammonia.
Silica gel refers to Merck silica gel 60 Art number 7734.
Flash silica gel refers to Merck silica gel 60 Art number 9385.
- 15 Biotage refers to prepacked silica gel cartridges containing KP-Sil run on flash 12i chromatography module.
Bond Elut are prepacked cartridges used in parallel purifications, normally under vacuum. These are commercially available from Varian.
SCX refers to prepacked SPE cartridges containing benzenesulphonic acid ion
- 20 exchange resin.
Preparative thin layer chromatography was carried out on silica gel, 20x20cm, Whatman PK6F, 60A, 1mm thick.
- 25 LC was conducted on a Luna 3 μ m C18(2) column (50mm x 2mm id) eluting with 0.05% v/v trifluoroacetic acid in water (solvent A) and 0.05% v/v trifluoroacetic acid in acetonitrile (solvent B) using the elution gradient 0-8.0 min 0%B-95%B, 8.0-8.01min 95%B-0%B, with a flow rate of 1mL/min with a column temperature of 40°C.
- 30 LCMS was conducted on a Supelcosil LCABZ+PLUS column (3.3 cm x 4.6 mm ID) eluting with 0.1% HCO₂H and 0.01 M ammonium acetate in water (solvent A), and 0.05% HCO₂H 5% water in acetonitrile (solvent B), using the following elution gradient 0-0.7 min 0%B, 0.7-4.2 min 100%B, 4.2-5.3 min 0%B, 5.3-5.5 min 0%B at a flow rate of 3 ml/min. The mass spectra were recorded on a Fisons VG Platform spectrometer using electrospray positive and negative mode (ES+ve and ES-ve).

HPLC was conducted using the same chromatographic system as for the LCMS.

5 The XRPD analysis shown in the Figures were performed on a Phillips X pert Prop powder diffractometer, Model PW3040/60, serial number DY1379. The method runs from 2 to 45 degrees 2Theta with 0.02 degree 2Theta step size and a 2 second collection time at each step.

Example 1

10 Synthesis of N-[3-[(2-[[6-[(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)-phenyl]ethyl]amino)hexyl]oxy]ethoxy)methyl]phenyl]-N'-phenylurea acetate

i) Di(tert-butyl) 2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxoethylimidodicarbonate

Caesium carbonate (70.4g) was added to a stirred suspension of 2-bromo-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanone, (Glaxo, DE 3513885, 1985) (61.8g) and di-
15 t-butyl iminodicarboxylate (47.15g) in acetonitrile (600ml) under nitrogen. After vigorous stirring at 21° for 24 h the mixture was diluted with water (ca800ml) and the product was extracted with diethyl ether (1litre, then 200ml). The combined organic layers were washed with brine, dried (MgSO₄) and concentrated to ca400ml. The white crystals
20 were collected by filtration, washed with diethyl ether and dried to give the *title compound* (24.4g) δ (CDCl₃) 7.78(1H, dd, J 8, 2Hz), 7.65 (1H, brs), 6.87(1H, d, J 8Hz), 4.97(2H, s), 4.88(2H, s), 1.56(6H, s) and 1.48 (18H, s). Further concentration of the mother liquors gave additional product (13.8g). A third crop (7.1g) was obtained by chromatographing the mother liquors on silica gel, evaporating the appropriate eluate
25 and triturating with diethyl ether.

ii) tert-Butyl 2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxoethylcarbamate

Trifluoroacetic acid (92ml) was added to a stirred solution of di(tert-butyl) 2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxoethylimidodicarbonate, (352.55g) in
30 dichloromethane (3.6litres) at 21° and the reaction was stirred for 1.5 h. Aqueous NaOH solution (1.75litres) was added and after 10 min the phases were separated. The organic layer was washed with water, dried (MgSO₄) and evaporated to an oil. This was stored under high vacuum overnight and then triturated with hexane:ether (3:1) to

give the crude product (226.61g). This was purified by recrystallisation from diethyl ether to give the *title compound* (122.78g). Further product (61.5g) was obtained from the mother liquors by evaporation and chromatography on a Biotage using 15% EtOAc in hexane. LCMS RT = 3.37min.

5

iii) tert-Butyl (2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethylcarbamate

A 2M solution of borane - dimethyl sulphide in THF (28ml) was added slowly to a 1M solution of (R)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole in toluene (56ml) at 0° under nitrogen. A solution of tert-butyl 2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxoethylcarbamate, (108.2g) in THF (1.3litres) was added slowly keeping the temperature below 5° followed by 2M solution of borane - dimethyl sulphide in THF (252ml) over 50 min. After 1 h, 2M HCl (170ml) was added with cooling and the mixture was partitioned between EtOAc and water. The organic layer was washed with saturated NaHCO₃ solution and brine and dried (MgSO₄). The solution was concentrated and the product purified by chromatography on flash silica gel (800g), eluting successively with hexane:EtOAc (4:1 then 3:1) to give the *title compound* (93.3g), LCMS RT = 3.31min.

15

iv) (5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

tert-Butyl (2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethylcarbamate, (86.37g) in DMF (600ml) was added dropwise to a stirred suspension of sodium hydride (60% oil dispersion, 11.9g) in DMF (160ml) with cooling such that the internal temperature remained at 0° under nitrogen. The mixture was stirred at 21° for 2 h. The mixture was recooled to 0° and 2M HCl (134ml) was added. The mixture was diluted with water and the product was extracted with EtOAc twice. The solution was washed with brine twice, dried (MgSO₄) and evaporated to give the *title compound* (63.55g). LCMS RT = 2.66min.

25

v) 2-([tert-Butyl(dimethyl)silyl]oxy)ethanol

Ethylene glycol (2.00g) in anhydrous THF (60ml) under nitrogen was treated portionwise with sodium hydride (60% dispersion in mineral oil, 1.29g) and the mixture stirred at 20°C for 45min. Tert-butyl dimethylsilyl chloride (4.86g) was added and the mixture stirred at 20°C for 45min. Phosphate buffer (60ml, pH6.5) was added and the mixture stirred for 20 min before extracting with ether (60ml). The organic layer was

30

then washed with water (60ml) and brine (60ml), before drying over Na₂SO₄, filtering, and removing the solvent *in vacuo*. This was purified by flash chromatography on silica. Elution with 1:4 EtOAc/cyclohexane followed by solvent evaporation *in vacuo* gave the *title compound* (3.82g). TSP+ve 194 MNH₄⁺.

5

vi) {2-[(6-Bromohexyl)oxy]ethoxy}(tert-butyl)dimethylsilane

2-[[tert-Butyl(dimethyl)silyl]oxy]ethanol (1.82g), 1,6-dibromohexane (7.56g) and tetrabutylammonium bromide (0.067g) were stirred under nitrogen and treated with 50%w/v sodium hydroxide (2g in 4ml). The mixture was stirred vigorously at 20°C for 5
10 days. Water (100ml) was added, and the product extracted with dichloromethane (3x50ml). The combined organic layer was separated and dried over Na₂SO₄ before filtering. The solvent was evaporated *in vacuo* to give a residue which was purified by flash chromatography on silica. Elution with 5% ether/cyclohexane followed by solvent evaporation *in vacuo* gave the *title compound* (2.35g). LCMS RT = 4.32min, ES +ve
15 339 (MH)⁺.

vii) (5R)-3-[6-(2-[(tert-Butyl(dimethyl)silyl]oxy)ethoxy)hexyl]-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

A solution of (5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one
20 (0.83g) in DMF (20ml) was treated with sodium hydride (60% dispersion in mineral oil, 0.20g) and the mixture stirred under nitrogen at 20°C for 30 min. A solution of {2-[(6-bromohexyl)oxy]ethoxy}(tert-butyl)dimethylsilane (1.47g) in DMF (4ml) was added and the mixture stirred at 20°C for 90min. Phosphate buffer (20ml, pH6.5) was added,
25 before partitioning between EtOAc (50ml) and water (50ml). The layers were separated and the aqueous layer re-extracted with EtOAc (3x30ml). The combined organic layer was washed with water (3x50ml) and dried over Na₂SO₄ before filtering. Solvent evaporation *in vacuo* gave a residue which was purified by flash chromatography on silica. Elution with EtOAc-cyclohexane (1:1) followed by solvent evaporation *in vacuo* gave the *title compound* (0.84g). LCMS RT = 4.11min, ES+ve 507 (MH)⁺.

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viii) (5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-3-[6-(2-hydroxyethoxy)hexyl]-1,3-oxazolidin-2-one

A solution of (5R)-3-[6-(2-[[tert-butyl(dimethyl)silyl]oxy]ethoxy)hexyl]-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (0.79g) in THF (30ml) was treated with tetrabutylammonium fluoride on silica gel (3.08g) and the mixture stirred under nitrogen at 20°C for 2.75h. The reaction mixture was filtered and the filtrate evaporated *in vacuo* to give a residue which was purified by SPE on silica. Elution with dichloromethane, then EtOAc followed by solvent evaporation *in vacuo* gave the *title compound* (0.56g). LCMS RT = 3.05min, ES+ve 394 (MH)⁺.

ix) (5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-3-(6-{2-[(3-nitrobenzyl)oxy]ethoxy}hexyl)-1,3-oxazolidin-2-one

A solution of (5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-3-(6-(2-hydroxyethoxy)hexyl)-1,3-oxazolidin-2-one (0.20g) in DMF (5ml) was treated with sodium hydride (60% dispersion in mineral oil, 0.030g) and the mixture stirred under nitrogen at 20°C for 15 min. 3-nitrobenzylbromide (0.11g) was added, and the mixture stirred at 20°C for a further 3 h. Phosphate buffer (20ml, pH6.5) was added and the mixture was stirred for 5 min before extracting with EtOAc (3x20ml). The organic layer was washed with water (3x20ml), dried over Na₂SO₄ and filtered. Solvent evaporation gave the crude product which was purified by flash chromatography on silica. Elution with EtOAc-cyclohexane (7:3) followed by solvent evaporation *in vacuo* gave the *title compound* (0.10g). LCMS RT = 3.61min, ES+ve 529 (MH)⁺.

x) (5R)-3-(6-{2-[(3-Aminobenzyl)oxy]ethoxy}hexyl)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

A solution of (5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-3-(6-{2-[(3-nitrobenzyl)oxy]ethoxy}hexyl)-1,3-oxazolidin-2-one (0.10g) in EtOH (3ml) and EtOAc (3ml) was hydrogenated for 19.5h over platinum oxide (0.020g). The mixture was filtered through celite, and the solvent evaporated *in vacuo* to give a residue which was purified by flash chromatography on silica. Elution with EtOAc-cyclohexane (8:2) followed by solvent evaporation *in vacuo* gave the *title compound* (0.057g). LCMS RT = 3.43min, ES+ve 499 (MH)⁺.

xi) N-(3-[[2-[(6-[(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl)oxy]ethoxy)methyl]phenyl)-N'-phenylurea

A solution of (5R)-3-(6-{2-[(3-aminobenzyl)oxy]ethoxy}hexyl)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (0.057g) in dichloromethane (2ml) was treated

with phenyl isocyanate (0.020g) and the mixture stirred under nitrogen at 20°C for 2h. Isopropanol (5ml) was added to quench excess isocyanate, and the mixture stirred for 30min before leaving to stand for 15 h. The solvents were removed *in vacuo* to give a residue which was purified by SPE. Elution with a stepped gradient of eluants from
 5 cyclohexane to cyclohexane-EtOAc (9:1) and onwards to EtOAc followed by solvent evaporation *in vacuo* gave the *title compound* (0.062g). LCMS RT = 3.70min, ES+ve 618 (MH)⁺.

xii) N-[3-({2-[(6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]ethoxy)methyl}phenyl)-N'-phenylurea
 10 Potassium trimethylsilanolate (0.056g) was added to a solution of N-(3-{{2-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)-ethoxy)methyl}phenyl)-N'-phenylurea (0.061g) in degassed anhydrous THF (4ml) whilst stirring under nitrogen. The reaction mixture was heated to 65°C for 4 h, adding
 15 additional potassium trimethylsilanolate (0.057g) and heating for a further 2.5h, at which point the reaction mixture was cooled to room temperature. Phosphate buffer (20ml, pH6.5) was added and the mixture extracted with EtOAc (3x20ml). The combined organic layers were separated and dried over Na₂SO₄ before filtering. Solvent evaporation *in vacuo* gave the *title compound* (0.027g). LCMS RT = 2.80min, ES+ve
 20 592 (MH)⁺.

xiii) N-[3-({2-[(6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]-amino}hexyl)oxy]ethoxy)methyl}phenyl)-N'-phenylurea acetate
 25 A solution of N-[3-{{2-[(6-[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]ethoxy)methyl}phenyl)-N'-phenylurea (0.025g) in acetic acid (1ml) and water (0.5ml) were stirred under nitrogen at 70°C for 75min. The reaction mixture was cooled to room temperature before concentrating under vacuum and azeotroping with MeOH (2x10ml) to give the *title compound* (0.028g). LCMS RT = 2.50min, ES+ve 552 (MH)⁺.

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Example 2

Alternative synthesis of (5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-3-[6-[2-hydroxyethoxy]hexyl]-1,3-oxazolidin-2-one

35 i) [2-[(6-Bromohexyl)oxy]ethoxy)methyl]benzene

A solution of 2-(benzyloxy)ethanol (2.00g) and tetrabutylammonium bromide (84mg) in 1,6-dibromohexane (6.06ml) was treated with 50% w/v sodium hydroxide solution (5.0ml) and the mixture was vigorously stirred for 18h at 20°. Water (50ml) was added and the mixture was extracted with dichloromethane (40ml). The organic extract was dried (Na₂SO₄) and the solvent evaporated *in vacuo* to give a residue which was purified by flash chromatography on silica gel. Elution with EtOAc-PE (1:9) gave the *title compound* (2.87g). LCMS RT = 3.94min, ES +ve 337 (MNa)⁺, 339 (MNa)⁺

ii) 2-[(6-Bromohexyl)oxy]ethanol

A solution of [(2-[(6-bromohexyl)oxy]ethoxy)methyl]benzene (1.5g) in EtOAc (20ml) and EtOH (20ml) was hydrogenated over 10% palladium on carbon (200mg). After 2h the mixture was filtered through celite and the filtrate evaporated *in vacuo* to give the *title compound* (1.05g). TSP +ve 242 (MNH₄)⁺, 244 (MNH₄)⁺

iii) (5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-3-[6-[2-hydroxyethoxy]-hexyl]-1,3-oxazolidin-2-one

A solution of (5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (1.067g) in DMF (10ml) under nitrogen was treated with sodium hydride (60% dispersion in mineral oil, 222mg) and the mixture was stirred at 20° for 15min. A solution of 2-[(6-bromohexyl)oxy]ethanol (1.157g) in DMF (1ml) was added and the mixture was stirred at 20° for 3.5h. Phosphate buffer solution (pH 6.5, 20ml) and water (30ml) were added. The mixture was extracted with EtOAc (2x20ml) and the combined extracts were washed with water (30ml) and dried (Na₂SO₄). Solvent evaporation *in vacuo* gave a residue which was purified by flash chromatography on silica gel. Elution with MeOH-EtOAc (1:9) gave the *title compound* (1.42g). LCMS RT = 2.90min, ES +ve 394 (MH)⁺.

Example 3

Alternative synthesis of (5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-3-[6-[2-hydroxyethoxy]hexyl]-1,3-oxazolidin-2-one

i) (5R)-3-(6-Bromohexyl)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one
A solution of (5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (5.00g) and 1,6-dibromohexane (9.26ml) in DMF (50ml) at 0° under nitrogen was treated in three equal portions with sodium hydride (60% dispersion in mineral oil, 963mg). The

mixture was stirred at 0° for 30min and then at 20° for a further 2.5h. Phosphate buffer solution (pH 6.5, 50ml) and water (150ml) were added and the mixture was extracted with diethyl ether (2x150ml). The combined extracts were washed with water (2x150ml) and were dried (Na₂SO₄). The solvent was evaporated *in vacuo* and the residue was

5 purified by flash chromatography on silica gel. Elution with MeOH-dichloromethane (1:4) gave the *title compound* (7.10g). LCMS RT = 3.52min, ES +ve 412 (MH)⁺, 414 (MH)⁺.

10 ii) (5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-3-[6-[2-hydroxyethoxy]hexyl]-1,3-oxazolidin-2-one

A solution of ethylene glycol (5.00ml) in DMF (40ml) under nitrogen at 0° was treated portionwise with sodium hydride (60% dispersion in mineral oil, 1.292g) and the mixture was stirred at 0° for 15min. A solution of (5R)-3-(6-bromohexyl)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (7.40g) in DMF (10ml) was added. The mixture

15 was stirred at 0° for 0.5h then at 20° for 3h. Phosphate buffer solution (pH 6.5, 40ml) and water (160ml) were added and the mixture was extracted with EtOAc (2x100ml). The combined extracts were washed with water (2x150ml), brine (50ml) and were dried (Na₂SO₄). The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography on silica gel. Elution with MeOH-EtOAc (1:9) gave the *title compound*

20 (4.10g). LCMS RT = 2.90min, ES +ve 394 (MH)⁺.

Example 4

Synthesis of 4-[(1R)-2-[(6-[2-[(2,6-dichlorobenzyl)oxy]ethoxy]hexyl)amino]-1-hydroxyethyl]-2-(hydroxymethyl)phenol acetate

25 i) (5R)-3-(6-[2-[(2,6-Dichlorobenzyl)oxy]ethoxy]hexyl)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

A solution of (5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-3-[6-(2-hydroxyethoxy)hexyl]-1,3-oxazolidin-2-one (200mg) in DMF (4ml) under nitrogen was

30 treated with sodium hydride (26mg, 60% in oil) and the mixture was stirred at 20° for 10min. 2,6-Dichlorobenzyl bromide (122mg) was added and the mixture was stirred at 20° for 3h. Phosphate buffer solution (20ml, pH6.5) was added and the mixture was extracted with EtOAc (30ml). The extract was washed with water (2x20ml), dried (NaSO₄) and the solvent evaporated *in vacuo* to give a residue. The residue was

purified by chromatography on flash silica gel 20mm diameter column. Elution with EtOAc-cyclohexane (1:1) gave the *title compound* (155mg). LCMS RT = 3.97 min.

5 ii) (1R)-2-[(6-{2-[(2,6-Dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol

A solution of (5R)-3-(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (140mg) in THF (7ml) under nitrogen was treated with potassium trimethylsilanolate (130mg) and the mixture was heated (oil bath temperature 80°) with stirring for 3 h. The mixture was cooled to 20° and was
10 partitioned between phosphate buffer solution (20ml, pH6.5) and EtOAc (20ml). The organic phase was separated, dried (NaSO₄) and the solvent evaporated *in vacuo* to give the *title compound* (130mg). LCMS RT = 3.00 min.

15 iii) 4-[(1R)-2-[(6-{2-[(2,6-Dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl]-2-(hydroxymethyl)phenol acetate

A solution of (1R)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol (130mg) in acetic acid (2ml) and water (1ml) was heated (oil bath temperature 80°) with stirring for 30 min. The mixture was cooled to 20° and the solvent was evaporated *in vacuo*. The residue was azeotroped *in vacuo* with
20 MeOH (2x1ml) to give the *title compound* (135mg). LCMS RT = 2.57 min, ES +ve 486 (MH)⁺, 488 (MH)⁺, 490 (MH)⁺.

Example 5

25 Synthesis of N-(1,1'-biphenyl-4-yl)-N'-(3-[(2-[(6-[(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino]hexyl]oxy]ethoxy)methyl]phenyl)urea

i) N-(1,1'-Biphenyl-4-yl)-N'-(3-[(2-[(6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl]oxy]ethoxy)methyl]phenyl)urea

A solution of (5R)-3-(6-{2-[(3-aminobenzyl)oxy]ethoxy}hexyl)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (0.202g) in dichloromethane (4ml) was treated with 4-biphenyl isocyanate (0.126g) and the mixture stirred under nitrogen at 20°C for 19 h. Isopropanol (15ml) was added to quench excess isocyanate, and the mixture stirred for 2 h. The solvents were removed *in vacuo* to give a residue which was purified by Biotage. Elution with 6:4 EtOAc/cyclohexane followed by solvent

evaporation *in vacuo* gave the *title compound* (0.119g). LCMS RT = 4.09min, ES+ve 694 (MH)⁺.

ii) N-(1,1'-Biphenyl-4-yl)-N'-[3-[(2-[(6-[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino)hexyl]oxy]ethoxy)methyl]phenyl]urea

Potassium trimethylsilanolate (0.090g) was added to a solution of N-(1,1'-biphenyl-4-yl)-N'-[3-[(2-[(6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl]oxy)ethoxy)methyl]phenyl]urea (0.119g) in deoxygenated anhydrous THF (4ml) whilst stirring under nitrogen. The reaction mixture was heated to 65°C for 3h, at which point the reaction mixture was cooled to room temperature. Phosphate buffer (25ml, pH6.5) was added and the mixture extracted with EtOAc (3x25ml). The combined organic layers were separated and dried over Na₂SO₄ before filtering. Solvent evaporation *in vacuo* gave a residue which was purified by Biotage. Elution with 150:8:1 dichloromethane:EtOH:ammonia followed by solvent evaporation *in vacuo* gave the *title compound* (0.092g). LCMS RT = 3.16min, ES+ve 668 (MH)⁺.

iii) N-(1,1'-Biphenyl-4-yl)-N'-[3-[(2-[(6-[(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy]ethoxy)methyl]phenyl]urea acetate

A solution of N-(1,1'-biphenyl-4-yl)-N'-[3-[(2-[(6-[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino)hexyl]oxy]ethoxy)methyl]phenyl]urea (0.089g) in acetic acid (4ml) and water (2ml) were stirred under nitrogen at 70°C for 30min. The reaction mixture was cooled to room temperature before concentrating under vacuum and azeotroping with MeOH (2x10ml) to give the *title compound* (0.097g). LCMS RT = 3.08min, ES+ve 628 (MH)⁺.

Example 6

Synthesis of N-cyclohexyl-N'-[3-[(2-[(6-[(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy]ethoxy)methyl]phenyl]urea

i) N-Cyclohexyl-N'-[3-[(2-[(6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl]oxy)ethoxy)methyl]phenyl]urea

A solution of (5R)-3-(6-{2-[(3-aminobenzyl)oxy]ethoxy}hexyl)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (0.209g) in dichloromethane (4ml) was treated with cyclohexyl isocyanate (0.075g) and the mixture stirred under nitrogen at 20°C for 3h. At this point further cyclohexyl isocyanate (0.150g) was added, and the reaction

mixture stirred for a further 65h. Isopropanol (15ml) was added to quench excess isocyanate, and the mixture stirred for 3 h. The solvents were removed *in vacuo* to give a residue which was purified by Biotage. Elution with 6:4 EtOAc/cyclohexane followed by solvent evaporation *in vacuo* gave the *title compound* (0.212g). LCMS RT = 3.77min, ES+ve 624 (MH)⁺.

ii) *N*-Cyclohexyl-*N'*-[3-({2-[(6-[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino)hexyl]oxy]ethoxy)methyl]phenyl]urea

Potassium trimethylsilanolate (0.177g) was added to a solution of *N*-cyclohexyl-*N'*-[3-{{2-[(6-[(5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl]oxy)ethoxy)methyl]phenyl]urea (0.207g) in deoxygenated anhydrous THF (6ml) whilst stirring under nitrogen. The reaction mixture was heated to 65°C for 4.5h, at which point the reaction mixture was cooled to room temperature. Phosphate buffer (25ml, pH6.5) was added and the mixture left to stir for 10min before extracting with EtOAc (3x25ml). The combined organic layers were separated and dried over Na₂SO₄ before filtering. Solvent evaporation *in vacuo* gave a residue which was purified by Biotage. Elution with 150:8:1 dichloromethane:EtOH:ammonia followed by solvent evaporation *in vacuo* gave the *title compound* (0.138g). LCMS RT = 2.87min, ES+ve 598 (MH)⁺.

iii) *N*-Cyclohexyl-*N'*-[3-({2-[(6-[(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy]ethoxy)methyl]phenyl]urea triacetate

A solution of *N*-cyclohexyl-*N'*-[3-({2-[(6-[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino)hexyl]oxy]ethoxy)methyl]phenyl]urea (0.138g) in acetic acid (4ml) and water (1ml) were stirred under nitrogen at 70°C for 45min. The reaction mixture was cooled to room temperature before concentrating under vacuum and azeotroping with MeOH (3x10ml) to give a residue which was purified by Biotage. Elution with 50:8:1 dichloromethane:EtOH:ammonia followed by solvent evaporation *in vacuo* gave the *title compound* (0.126g). LCMS RT = 2.65min, ES+ve 558 (MH)⁺.

The following examples 7 to 9 and 11 to 20 were prepared similarly:

Example 7

4-[(1R)-2-[(6-[2-(Benzyloxy)ethoxy]hexyl)amino]-1-hydroxyethyl]-2-(hydroxymethyl)phenol acetate.

LCMS RT = 2.47 min, ES+ve 418 (MH)⁺.

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Example 8

4-[(2-[(6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)-hexyl]oxy)ethoxy)methyl]benzenesulfonamide.

LCMS RT = 2.18 min, ES+ve 497 (MH)⁺.

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Example 9

4-[(1R)-1-Hydroxy-2-[(6-[2-[(4-iodobenzyl)oxy]ethoxy]hexyl)amino]ethyl]-2-(hydroxymethyl)phenol acetate.

LCMS RT = 2.64 min, ES+ve 544 (MH)⁺.

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Example 10

3-[(2-[(6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy)ethoxy)methyl]benzenesulfonamide acetate

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i) 3-(Hydroxymethyl)-N,N-bis[[2-(trimethylsilyl)ethoxy)methyl]benzenesulfonamide

A solution of 3-(hydroxymethyl)benzenesulfonamide (670mg) in DMF (20ml) under nitrogen was treated with sodium hydride (315mg, 60% in oil) and the mixture was stirred at 20° for 15 min. The mixture was then treated with 2-

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(trimethylsilyl)ethoxymethyl chloride (1.27ml) and the mixture was stirred at 20° for 1 h. Phosphate buffer solution (50ml, pH6.5) was added and the mixture was extracted with EtOAc. The extract was washed with water, dried (Na₂SO₄) and the solvent evaporated *in vacuo* to give a residue. The residue was purified by chromatography on flash silica gel (40mm diameter column). Elution with EtOAc-cyclohexane (3:7) gave the *title compound* (985mg). LCMS RT = 3.84 min.

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ii) 3-[[2-[(6-[(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl]oxy)ethoxy)methyl]-N,N-bis[[2-(trimethylsilyl)ethoxy)methyl]benzenesulfonamide

A solution of 3-(hydroxymethyl)-N,N-bis{[2-(trimethylsilyl)ethoxy]methyl}benzenesulfonamide (512mg) in DMF (4ml) under nitrogen was treated with sodium hydride (1.295g, 60% in oil) and the mixture was stirred at 20° for 30 min. A solution of 2-({6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)ethyl methanesulfonate (359mg) in DMF (1ml) was added and the mixture was stirred at 20° for 18 h. Phosphate buffer solution (25ml, pH6.5) was added and the mixture was extracted with EtOAc. The extract was washed with water, dried (Na₂SO₄) and the solvent evaporated *in vacuo* to give a residue. The residue was purified by chromatography on flash silica gel (30mm diameter column). Elution with EtOAc-cyclohexane (2:3) then (1:1) gave the *title compound* (400mg). LCMS RT = 4.43 min.

iii) 3-({2-[(6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino)hexyl]oxy}ethoxy)methyl)-N,N-bis{[2-(trimethylsilyl)ethoxy]methyl}benzenesulfonamide

A solution of 3-({2-[(6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl]oxy}ethoxy)methyl)-N,N-bis{[2-(trimethylsilyl)ethoxy]methyl}benzenesulfonamide (200mg) in THF (10ml) under nitrogen was treated with potassium trimethylsilanolate (125mg) and the mixture heated to 70° for 5 h. The mixture was cooled to 20° and phosphate buffer solution (25ml, pH6.5) was added. The mixture was extracted with EtOAc, the extract dried (Na₂SO₄) and the solvent evaporated *in vacuo* to give the *title compound* (400mg). LCMS RT = 3.6 min.

iv) 3-[(2-[(6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy}ethoxy)methyl]benzenesulfonamide acetate

A solution of 3-({2-[(6-[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino)hexyl]oxy}ethoxy)methyl)-N,N-bis{[2-(trimethylsilyl)ethoxy]methyl}benzenesulfonamide (170mg) in acetic acid (8ml) and water (4ml) was heated to 70° for 6 h. The mixture was cooled to 20° and the solvent evaporated *in vacuo*. The residue was purified by preparative TLC. Elution with dichloromethane-EtOH-0.880 ammonia (25:8:1) gave the free base (35mg). This was

dissolved in acetic acid (2ml) and the solvent evaporated *in vacuo* to give the *title compound* (40mg). LCMS RT = 2.13 min, ES +ve 497 (MH)⁺

Example 11

- 5 2-(Hydroxymethyl)-4-((1R)-1-hydroxy-2-{[6-(2-[(1R)-1-phenylethyl]oxy)ethoxy]-hexyl}amino)ethyl)phenol acetate.
LCMS RT = 2.55 min, ES+ve 432 (MH)⁺.

Example 12

- 10 2-(Hydroxymethyl)-4-((1R)-1-hydroxy-2-{[6-(2-[(1S)-1-phenylethyl]oxy)ethoxy]-hexyl}amino)ethyl)phenol acetate.
LCMS RT = 2.45 min, ES+ve 432 (MH)⁺.

Example 13

- 15 4-[(1R)-2-[(6-{2-[(4-Chlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl]-2-(hydroxymethyl)phenol acetate.
LCMS RT = 2.61 min, ES+ve 452 (MH)⁺, 454 (MH)⁺.

Example 14

- 20 2-(Hydroxymethyl)-4-[(1R)-1-hydroxy-2-[(6-{2-[(4-methylbenzyl)oxy]ethoxy}hexyl)amino]ethyl)phenol acetate.
LCMS RT = 2.56 min, ES+ve 432 (MH)⁺.

Example 15

- 25 4-[(1R)-2-[(6-{2-[(2,4-Dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl]-2-(hydroxymethyl)phenol acetate.
LCMS RT = 2.77 min, ES+ve 486 (MH)⁺, 488 (MH)⁺, 490 (MH)⁺.

Example 16

- 30 2-(Hydroxymethyl)-4-[(1R)-1-hydroxy-2-[(6-{2-[(4-(trifluoromethyl)benzyl]oxy]ethoxy}hexyl)amino]ethyl)phenol acetate
LCMS RT = 2.60 min, ES+ve 486 (MH)⁺.

Example 17

4-((1R)-1-Hydroxy-2-[(6-{2-[(3-hydroxybenzyl)oxy]ethoxy}hexyl)amino]ethyl)-2-(hydroxymethyl)phenol acetate.

LCMS RT = 2.31 min, ES+ve 434 (MH)⁺.

5 Example 18

N-{3-[(2-[(6-((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino)hexyl]oxy]ethoxy)methyl]phenyl}urea acetate.

LCMS RT = 2.30 min, ES+ve 476 (MH)⁺.

10 Example 19

N-{3-[(2-[(6-((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl]oxy]ethoxy)methyl]phenyl}-4-(methylsulfonyl)benzenesulfonamide acetate.

LCMS RT = 2.54 min, ES+ve 451 (MH)⁺.

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Example 20

N-{3-[(2-[(6-((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino)hexyl]oxy]ethoxy)methyl]phenyl}methanesulfonamide acetate.

LCMS RT = 2.42 min, ES+ve 511 (MH)⁺.

20 Example 21

Synthesis of N-{3-[(3-[(2-[(6-((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl]oxy]ethoxy)methyl]phenyl)amino)carbonyl]amino}phenyl)pyridine-3-carboxamide

25 i) 2-((3-Nitrophenyl)methoxy)ethanol

Ethylene glycol (7.18g) in anhydrous DMF (50ml) was treated at 0° under nitrogen with sodium hydride (60% dispersion in mineral oil, 1.85g) and the mixture stirred for 30 min. 3-Nitrobenzyl bromide (5.00g) was added and the mixture was warmed to 20° over 1h and stirred for a further 15 h. Phosphate buffer (pH 6.5, 100ml) and water (100ml) were added and the product was extracted with EtOAc (2x150ml). The combined organic layer was washed with water (2x200ml) and dried (Na₂SO₄). Solvent evaporation *in vacuo* gave a residue that was purified by Biotage. Elution with EtOAc-PE (1:1 then 2:1) followed by solvent evaporation *in vacuo* gave the *title compound* (16.34g) HPLC RT = 1.554min. TSP+ve 215 (MNH₄)⁺.

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ii) 1-[(2-[(6-Bromohexyl)oxy]ethoxy)methyl]-3-nitrobenzene

2-[(3-Nitrophenyl)methoxy]ethanol (6.50g), 1,6-dibromohexane (24.2g) and tetrabutylammonium bromide (0.21g) were stirred under nitrogen at 20° and treated with 50%w/v sodium hydroxide (10ml). The mixture was stirred vigorously for 19 h before water (150ml) was added. The product was extracted with dichloromethane (3x80ml) and the combined organic layer was dried (Na₂SO₄). Solvent evaporation *in vacuo* gave a residue that was purified by Biotage. Elution with PE-EtOAc (1:0 then 3:1) followed by solvent evaporation *in vacuo* gave the *title compound* (8.12g). HPLC RT = 3.238min.

iii) (5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-3-{6-[2-[(3-nitrophenyl)methoxy]ethoxy]hexyl}-1,3-oxazolidin-2-one

A solution of (5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (4.40g) in anhydrous DMF (75ml) was treated under nitrogen at 0° with sodium hydride (60% dispersion in mineral oil, 1.04g) and the mixture stirred for 40 min. A solution of 1-[(2-[(6-bromohexyl)oxy]ethoxy)methyl]-3-nitrobenzene (8.12g) in DMF (10ml) was added and the mixture stirred at 20° for 2 h. Phosphate buffer (pH 6.5, 100ml) and water (100ml) were added and the product extracted with EtOAc (4x100ml). The combined organic layer was washed with water (3x100ml) and dried (Na₂SO₄). The solvent was removed *in vacuo* to give a residue that was purified by Biotage. Elution with EtOAc-PE (1:1 then 3:2) followed by solvent evaporation *in vacuo* gave the *title compound* (9.50g). LCMS RT = 3.75min, ES +ve 529 (MH)⁺.

iv) (5R)-3-{6-[2-[(3-Aminophenyl)methoxy]ethoxy]hexyl}-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

A solution of (5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-3-{6-[2-[(3-nitrophenyl)methoxy]ethoxy]hexyl}-1,3-oxazolidin-2-one (9.50g) in EtOAc (120ml) and EtOH (120ml) was hydrogenated over platinum oxide (0.20g) for 1.75 h. The mixture was filtered through celite and washed with EtOH. Solvent evaporation *in vacuo* gave the *title compound* (9.60g). LCMS RT = 3.25 min, ES +ve 499 (MH)⁺.

v) N-[3-{2-[(6-[(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl)oxy]ethoxy)methyl}phenyl]-N'-(3-nitrophenyl)urea

A solution of (5R)-3-{6-[2-[(3-aminophenyl)methoxy]ethoxy]hexyl}-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (1.00g) in anhydrous dichloromethane (15ml)

was treated under nitrogen at 20° with 3-nitrophenyl isocyanate (0.43g) and the mixture stirred for 4 h. Isopropanol (20ml) was added and the mixture stirred for 17 h before the solvent was removed *in vacuo* to give a residue that was purified by Biotage. Elution with dichloromethane-EtOH-ammonia (325:8:1) followed by solvent evaporation *in vacuo* gave the *title compound* (1.13g). LCMS RT = 3.85 min, ES +ve 663 (MH)⁺.

vi) N-(3-Aminophenyl)-N'-[3-({2-({6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)ethoxy)methyl}phenyl]urea

A solution of N-[3-({2-({6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)ethoxy)methyl}phenyl]-N'-(3-nitrophenyl)urea (0.976g) in EtOH (12ml) and EtOAc (12ml) was hydrogenated over platinum oxide (0.020g) for 2 h. The mixture was filtered through celite and washed with EtOH. Solvent evaporation *in vacuo* gave the *title compound* (0.93g). LCMS RT = 3.48 min, ES +ve 633 (MH)⁺.

vii) N-[3-({[3-({2-({6-[(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)ethoxy)methyl}phenyl]amino)carbonyl]amino]-phenyl]pyridine-3-carboxamide

A solution of N-(3-aminophenyl)-N'-[3-({2-({6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)ethoxy)methyl}phenyl]-urea (0.20g) in pyridine (4ml) was treated under nitrogen at 20° with nicotinoyl chloride hydrochloride (0.118g) and the mixture stirred for 5.5 h. Sat. sodium bicarbonate solution (25ml) was added and the product was extracted with dichloromethane (3x20 ml). The combined organic layer was dried (Na₂SO₄) and the solvent removed *in vacuo* to give a residue that was purified by SPE. Elution with dichloromethane-EtOAc (1:0, 1:1, then 0:1), then MeOH-EtOAc (1:50), followed by solvent evaporation *in vacuo* gave the *title compound* (0.209g). LCMS RT = 3.54 min, ES +ve 738 (MH)⁺.

viii) N-(3-({[3-({2-({6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl}oxy)ethoxy)methyl}phenyl]amino)carbonyl]amino)-phenyl]pyridine-3-carboxamide

A solution of N-[3-({[3-({2-({6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)ethoxy)methyl}phenyl]amino)carbonyl]-amino]phenyl]pyridine-3-carboxamide (0.209g) in anhydrous THF (10ml) was treated under nitrogen at 20° with potassium trimethylsilanolate (0.217g). The mixture was heated to 65° for 2.5 h before cooling to room temperature. Phosphate buffer (pH 6.5, 25ml) was added and

the product extracted with EtOAc (3x20ml). Solvent evaporation *in vacuo* gave a residue that was purified by SPE. Elution with dichloromethane-EtOH-ammonia (100:8:1 then 50:8:1) followed by solvent evaporation *in vacuo* gave the *title compound* (0.109g). LCMS RT = 2.86 min, ES +ve 712 (MH)⁺.

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ix) N-(3-[[[3-[(2-[[6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy]ethoxy)methyl]phenyl]amino)carbonyl]amino)phenyl)-pyridine-3-carboxamide

A solution of N-(3-[[[3-[(2-[[6-[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino)hexyl]oxy]ethoxy)methyl]phenyl]amino)carbonyl]amino)-phenylpyridine-3-carboxamide (0.109g) in acetic acid (4ml) and water (2ml) was heated to 68° for 30 min. The mixture was cooled to room temperature before concentrating *in vacuo* to leave a residue that was purified by Biotage. Elution with dichloromethane-EtOH-ammonia (25:8:1) followed by solvent evaporation *in vacuo* gave the *title compound* (0.089g). LCMS RT = 2.02 min, ES +ve 672 (MH)⁺.

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Example 22

Synthesis of N-cyclohexyl-3-[(2-[[6-[(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy]ethoxy)methyl]benzenesulfonamide compound with (2E)-but-2-enedioic acid (2:1)

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i) 3-[(Cyclohexylamino)sulfonyl]benzoic acid

A mixture of 3-(chlorosulfonyl)benzoic acid (2.00g) and dichloromethane (20ml) under nitrogen at 0° was treated with cyclohexylamine (3.63ml) and the mixture was stirred at 0° for 0.5 h. The solvent was evaporated *in vacuo* and the residue was treated with 1M potassium hydrogen sulfate solution (50ml) and extracted with EtOAc (3x50ml). The combined extracts were dried (Na₂SO₄) and the solvent evaporated *in vacuo* to give the *title compound* (2.28g). LCMS RT = 3.16min, ES +ve 284 (MH)⁺.

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ii) N-Cyclohexyl-3-(hydroxymethyl)benzenesulfonamide

A solution of 3-[(cyclohexylamino)sulfonyl]benzoic acid (2.25g) in THF (100ml) under nitrogen at 0° was treated dropwise with 1M borane-THF solution (23.82ml). The mixture was stirred at 0° for 0.5 h and then at 20° for 72 h. The mixture was cooled to 0° and MeOH (20ml) was added dropwise. The mixture was stirred for 15 min and then 2N hydrochloric acid (50ml) was added and the mixture was allowed to warm to 20°. The bulk of the organic solvents were removed by evaporation *in vacuo* and the residual

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aqueous phase was extracted with EtOAc (2x40ml). The combined extracts were dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The residue was purified by SPE on alumina (10g, activated, neutral, Brockmann 1). Elution with MeOH-dichloromethane (1:20) gave the *title compound* (1.944g). LCMS RT = 2.95min, ES +ve 270 (MH)⁺.

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iii) N-Cyclohexyl-3-(hydroxymethyl)-N-({2-(trimethylsilyl)ethoxy)methyl}-benzenesulfonamide

A solution of N-cyclohexyl-3-(hydroxymethyl)benzenesulfonamide (1.744g) in DMF (30ml) under nitrogen was treated with sodium hydride (60% dispersion in mineral oil, 311mg) and the mixture stirred at 20° for 0.5 h. 2-(Trimethylsilyl)ethoxymethyl chloride (1.15ml) was added and the mixture was stirred for a further 2 h at 20°. Phosphate buffer solution (pH 6.5, 50ml) and water (50ml) were added and the mixture was extracted with EtOAc (2x50ml). The combined extracts were washed with water (2x100ml) and dried (Na_2SO_4). Solvent evaporation *in vacuo* gave a residue which was purified by flash chromatography on silica gel. Elution with EtOAc-PE (3:7) gave the *title compound* (1.917g). LCMS RT = 3.83min, ES +ve 417 (MNH₄)⁺.

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iv) 2-({6-[(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)ethyl methanesulfonate

A solution of (5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-3-{6-[2-hydroxyethoxy]hexyl}-1,3-oxazolidin-2-one (200mg) in dichloromethane (14ml) under nitrogen at 0° was treated with diisopropylethylamine (0.10ml) followed by methanesulfonyl chloride (0.04ml). The mixture was stirred at 0° for 0.5 h and sat. sodium bicarbonate solution (30ml) was then added. The mixture was extracted with dichloromethane (30ml) and the organic extract dried (Na_2SO_4). The solvent was evaporated *in vacuo* to give the *title compound* (240mg). LCMS RT = 3.22min, ES +ve 472 (MH)⁺.

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v) N-Cyclohexyl-3-({2-({6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)ethoxy)methyl}-N-({2-(trimethylsilyl)ethoxy)methyl}-benzenesulfonamide

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A solution of N-cyclohexyl-3-(hydroxymethyl)-N-({2-(trimethylsilyl)ethoxy)methyl}benzenesulfonamide (508mg) in DMF (8ml) under nitrogen at 20° was treated with sodium hydride (60% dispersion in mineral oil, 58mg) and the mixture was stirred 15 min. A solution of 2-({6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-

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oxazolidin-3-yl]hexyl]oxy)ethyl methanesulfonate (400mg) in DMF (2ml) was added and the mixture was stirred at 20° for 72h. Phosphate buffer solution (pH 6.5, 10ml) and water (20ml) were added and the mixture was extracted with EtOAc (30ml). The extract was washed with water (2x30ml), dried (Na₂SO₄) and the solvent evaporated *in vacuo*.

- 5 The residue was purified by flash chromatography on silica gel. Elution with EtOAc-PE (1:1) gave the *title compound* (530mg). LCMS RT = 4.47min, ES +ve 793 (MH)⁺.

- vi) N-Cyclohexyl-3-[(2-[(6-[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino)hexyl]oxy)ethoxy)methyl]-N-[(2-(trimethylsilyl)ethoxy)methyl]benzenesulfonamide
 10 The *title compound* was prepared by a procedure similar to that described in Example 1xii). LCMS RT = 3.58min, ES +ve 749 (MH)⁺.

- vii) N-Cyclohexyl-3-[(2-[(6-[(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)-phenyl]ethyl]amino)hexyl]oxy)ethoxy)methyl]benzenesulfonamide compound with (2E)-but-2-enedioic acid (2:1)
 15 A solution of N-cyclohexyl-3-[(2-[(6-[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino)hexyl]oxy)ethoxy)methyl]-N-[(2-(trimethylsilyl)ethyl]oxy)methyl]benzenesulfonamide (350mg) in acetic acid (20ml) and water (10ml)
 20 was heated to 70° for 1 h. The mixture was cooled to 20° and the solvent was evaporated *in vacuo*. The residue was azeotroped with MeOH (2x10ml) and the residue was purified by preparative TLC. Elution with dichloromethane-EtOH-ammonia (25:8:1) gave the free base (200mg). This was dissolved in EtOH (5ml) and treated with a solution of fumaric acid (20mg) in EtOH (5ml). The solvent was evaporated *in vacuo*
 25 to give the *title compound* (216mg). LCMS RT = 2.70min, ES +ve 579 (MH)⁺.

Example 23

- Synthesis of N-[3-[(2-[(6-[(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)-phenyl]ethyl]amino)hexyl]oxy)ethoxy)methyl]phenyl]-3-[(phenylsulfonyl)amino]benzamide compound with (2E)-but-2-enedioic acid (2:1)
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i) N-[3-[(2-[(6-[(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl]oxy)ethoxy)methyl]phenyl]-3-nitrobenzamide

- A solution of (5R)-3-{6-[2-[(3-aminophenyl)methyl]oxy]ethoxy}hexyl)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (2.20g) in pyridine (20ml) under nitrogen was treated with 3-nitrobenzoyl chloride (819mg) and the mixture was stirred at 20° for 2.5 h. Sat. sodium bicarbonate solution (100ml) was added and the mixture was
 5 extracted with dichloromethane (2x50ml). The combined extracts were dried (Na₂SO₄) and the solvent evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel. Elution with EtOAc-PE (2:1) gave the *title compound* (2.11g). LCMS RT = 3.71min, ES +ve 648 (MH)⁺.
- 10 ii) 3-Amino-N-[3-({2-[(6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl]oxy)ethoxy)methyl]phenyl]benzamide
 A solution of N-[3-({2-[(6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl]oxy)ethoxy)methyl]phenyl]-3-nitrobenzamide (2.11g) in EtOAc (30ml) and EtOH (30ml) was hydrogenated over platinum oxide (100mg). After 1.25 h
 15 the mixture was filtered through celite and the filtrate evaporated *in vacuo* to give the *title compound* (1.955g). LCMS RT = 3.49min, ES +ve 618 (MH)⁺.
- iii) N-[3-({2-[(6-[(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl]oxy)ethoxy)methyl]phenyl]-3-[(phenylsulfonyl)amino]-benzamide
 20 3-Amino-N-[3-({2-[(6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl]oxy)ethoxy)methyl]phenyl]benzamide (200mg) in pyridine (5ml) under nitrogen was treated with benzenesulfonyl chloride (0.045ml) and the mixture was stirred at 20° for 2 h. Sat. sodium bicarbonate solution (30ml) was added and the mixture was extracted with dichloromethane (2x20ml). The combined extracts were
 25 dried (Na₂SO₄) and the solvent evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel. Elution with EtOAc-dichloromethane (1:1) gave the *title compound* (155mg). LCMS RT = 3.72min, ES +ve 758 (MH)⁺.
- iv) N-[3-({2-[(6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]-amino}hexyl]oxy)ethoxy)methyl]phenyl]-3-[(phenylsulfonyl)amino]benzamide
 30 The *title compound* was prepared by a procedure similar to that described in Example 1xii). LCMS RT = 2.96min, ES +ve 732 (MH)⁺.
- v) N-[3-({2-[(6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]-ethyl]amino}hexyl]oxy)ethoxy)methyl]phenyl]-3-[(phenylsulfonyl)amino]-benzamide
 35 compound with (2E)-but-2-enedioic acid (2:1)

The *title compound* was prepared by a procedure similar to that described in Example 22vii). LCMS RT = 2.71min, ES +ve 692 (MH)⁺.

Example 24

5 Synthesis of 4-[(1R)-2-({6-[2-({3-[(2,3-dihydroimidazo[2,1-b][1,3]thiazol-6-ylmethyl)amino]benzyl}oxy)ethoxy]hexyl}amino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol acetate (1:2)

10 i) (5R)-3-[6-(2-[(3-[(2,3-Dihydroimidazo[2,1-b][1,3]thiazol-6-ylmethyl)amino]-phenyl)methyl]oxy)ethoxy]hexyl]-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

A solution of (5R)-3-[6-(2-[(3-aminophenyl)methyl]oxy)ethoxy]hexyl]-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (200mg) and 2,3-dihydroimidazo[2,1-b][1,3]thiazole-6-carboxaldehyde (62mg) (WO94/10178) in dichloromethane (10ml) was
15 treated under nitrogen with sodium triacetoxy borohydride (340mg) and stirred at 20° for 1.5 h. The mixture was cooled to 0°, phosphate buffer solution (pH6.5, 20ml) was added and the mixture was extracted with EtOAc (3x30ml). The combined organic extracts were dried (Na₂SO₄) and the solvent evaporated *in vacuo* to give a residue which was purified by SPE. Elution with dichloromethane, dichloromethane-EtOH-ammonia (400:8:1) then (225:8:1) gave the *title compound* (172mg). LCMS RT =
20 3.16min, ES +ve 637 (MH)⁺.

25 ii) (1R)-2-[(6-[2-[(3-[(2,3-Dihydroimidazo[2,1-b][1,3]thiazol-6-ylmethyl)amino]-phenyl)methoxy]ethoxy]hexyl)amino)-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol
The *title compound* was prepared by a procedure similar to that described in Example 21viii). LCMS RT = 2.46min, ES +ve 611 (MH)⁺.

30 iii) 4-[(1R)-2-({6-[2-({3-[(2,3-Dihydroimidazo[2,1-b][1,3]thiazol-6-ylmethyl)amino]-benzyl}oxy)ethoxy]hexyl}amino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol acetate (1:2)
The *title compound* was prepared by a procedure similar to that described in Example 22vii). LCMS RT = 2.25min, ES +ve 571 (MH)⁺.

Example 25Synthesis of N-cyclopropyl-3'-[(2-[(6-[(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino]hexyl]oxy)ethoxy)methyl]-1,1'-biphenyl-2-sulfonamide acetate

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i) (5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-3-(6-[2-[(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methoxy)ethoxy]hexyl)-1,3-oxazolidin-2-one

A stirred mixture of (5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-3-{6-[2-[(3-iodophenyl)methoxy]ethoxy]hexyl}-1,3-oxazolidin-2-one (1.3g), bis(pinacolato)diboron (0.94g), potassium acetate (0.62g) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (complex with dichloromethane 1:1, 100mg) in DMF (25ml) under nitrogen was heated at 90° for 3.5 h. The mixture was cooled to 20°, poured into water (400ml) and extracted with EtOAc (3x50ml). The extracts were washed with water (200ml), dried (MgSO₄) and evaporated *in vacuo* to give a residue which was purified by Biotage. Elution with diethyl ether-PE (4:1) gave the *title compound* (920mg). LCMS RT = 3.93min, ES +ve 610 (MH)⁺.

ii) 1,1-Dimethylethyl (2-bromophenyl)sulfonyl(cyclopropyl)carbamate

Cyclopropylamine (1.7g) was added to a stirred solution of 2-bromobenzenesulfonyl chloride (2.0g) in THF (25ml) under nitrogen. The mixture was stirred at 0° for 20 min and the solvent was then evaporated *in vacuo*. The residue was then triturated with cold water (20ml), the mixture filtered and the filter cake dried *in vacuo*. The filter cake was then dissolved in dichloromethane (30ml) and treated with triethylamine (1.53ml) and 4-(dimethylamino)pyridine (90mg) with stirring under nitrogen. The mixture was cooled to 0° and was treated with di-*tert*-butyl dicarbonate (2.4g). The mixture was then stirred at 5° for 1h and then washed with 1N hydrochloric acid (40ml), water (50ml) and was dried (Na₂SO₄). The solvent was evaporated *in vacuo* and the residue was recrystallised from cyclohexane (30ml) to give the *title compound* (2.00g). LCMS RT = 3.52min, ES +ve 393 (MNH₄)⁺, 395 (MNH₄)⁺.

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iii) 1,1-Dimethylethyl cyclopropyl{[3'-[(2-[(6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl]oxy)ethoxy)methyl]-1,1'-biphenyl-2-yl]sulfonyl}carbamate

A stirred mixture of (5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-3-(6-[2-[(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methoxy)ethoxy]hexyl)-1,3-oxazolidin-2-

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- one (420mg), 1,1-dimethylethyl (2-bromophenyl)-sulfonyl(cyclopropyl)carbamate (341mg) and potassium carbonate (520mg) in dimethoxyethane (10ml) under nitrogen was treated with [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (complex with dichloromethane 1:1, 100mg) and the mixture heated under reflux for 18 h. The mixture was cooled to 20°, diluted with EtOAc (25ml) and filtered through celite. The filtrate was evaporated *in vacuo* to give a residue which was purified by Biotage. Elution with diethyl ether-PE (4:1) gave the *title compound* (262mg). LCMS RT = 4.15min, ES -ve 822 (MHCO₂)⁻.
- iv) N-Cyclopropyl-3'-[(2-[(6-[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino)hexyl]oxy]ethoxy)methyl]-1,1'-biphenyl-2-sulfonamide
A stirred mixture of 1,1-dimethylethyl cyclopropyl{[3'-[(2-[(6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl]oxy)ethoxy)methyl]-1,1'-biphenyl-2-yl]sulfonyl}carbamate (260mg) and potassium trimethylsilanolate (420mg) in THF (10ml) was heated under reflux for 2 h. The mixture was cooled to 20°, poured into phosphate buffer solution (pH6.5, 50ml) and extracted with EtOAc (3x30ml). The combined organic extracts were washed with water (50ml), dried (MgSO₄) and the solvent evaporated *in vacuo* to give a residue which was purified by Biotage. Elution with dichloromethane-ethanol-ammonia (100:8:1) gave the *title compound* (132mg). LCMS RT = 3.06min, ES +ve 653 (MH)⁺.
- v) N-Cyclopropyl-3'-[(2-[(6-[(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)-phenyl]ethyl]amino)hexyl]oxy]ethoxy)methyl]-1,1'-biphenyl-2-sulfonamide acetate
The *title compound* was prepared by a procedure similar to that described in Example 1xiii). LCMS RT = 2.75min, ES +ve 613 (MH)⁺.

Example 26

Synthesis of N-[3-[(2-[(6-[(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)-phenyl]ethyl]amino)hexyl]oxy]ethoxy)methyl]phenyl]-N'-(3-(phenylethynyl)phenyl)urea

30

i) N-[3-[(2-[(6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl]oxy]ethoxy)methyl]phenyl]-N'-(3-iodophenyl)urea

35

3-Iodophenylisocyanate (500mg) was added to a solution of (5R)-3-{6-[2-[(3-aminophenyl)methyl]oxy]ethoxy]hexyl}-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-

- oxazolidin-2-one (700mg) in dichloromethane (14ml) and the mixture was stirred at 20° under nitrogen for 5h. Isopropanol (14ml) was added and the mixture was stirred for 16h. The solvent was evaporated *in vacuo* to give a residue that was purified by Biotage. Elution with EtOAc-PE (2:1) gave the *title compound* (800mg). LCMS RT = 4.02min, ES +ve 744 (MH)⁺.
- 5
- ii) N-{3-[(2-[(6-[(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl)oxy]ethoxy)methyl]phenyl}-N'-[3-(phenylethynyl)phenyl]urea
 A solution of N-{3-[(2-[(6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl)oxy]ethoxy)methyl]phenyl}-N'-[3-(iodophenyl)urea (393mg) and phenylacetylene (77mg) in DMF (6ml) was treated with diisopropylethylamine (5ml) and nitrogen was passed through the solution for 5 min. Copper (I) iodide (10mg) and dichlorobis(triphenylphosphine)palladium(II) (47mg) were added and the mixture was stirred under nitrogen at 20° for 21.5 h. The solvent was evaporated *in vacuo* and EtOAc (15ml) was added. The supernatant solution was collected and the solvent evaporated *in vacuo* to give a residue which was purified by Biotage. Elution with dichloromethane-ethanol-ammonia (325:8:1) gave the *title compound* (328mg). LCMS RT = 3.93min, ES +ve 718 (MH)⁺.
- 10
- 15
- iii) N-{3-[(2-[(6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]-amino)hexyl]oxy]ethoxy)methyl]phenyl}-N'-[3-(phenylethynyl)phenyl]urea
 The *title compound* was prepared by a procedure similar to that described in Example 25iv). LCMS RT = 3.35min, ES +ve 692 (MH)⁺.
- 20
- iv) N-{3-[(2-[(6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]-amino)hexyl]oxy]ethoxy)methyl]phenyl}-N'-[3-(phenylethynyl)phenyl]urea
 A solution of N-{3-[(2-[(6-[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino)hexyl]oxy]ethoxy)methyl]phenyl}-N'-[3-(phenylethynyl)-phenyl]urea (242mg) in MeOH (8ml) was loaded under gravity onto an SCX cartridge which had been pre-conditioned with MeOH. Elution with MeOH then ammonia-MeOH (15:100) gave a residue which was passed through an SCX cartridge as described above two more times. The resulting residue was purified by Biotage. Elution with dichloromethane-ethanol-ammonia (50:8:1) gave the *title compound* (145mg). LCMS RT = 3.34min, ES +ve 652 (MH)⁺.
- 25
- 30
- 35

Example 27

Synthesis of N-{3-[(2-{[6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)-phenyl]ethyl)amino)hexyl]oxy}ethoxy)methyl]phenyl}-N'-[3-(2-phenylethyl)-phenyl]urea compound with (2E)-but-2-enedioic acid (3:2)

5

A solution of N-{3-[(2-{[6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)-phenyl]ethyl)amino)hexyl]oxy}ethoxy)methyl]phenyl}-N'-[3-(phenylethynyl)-phenyl]urea (70mg) in EtOH (15ml) was hydrogenated over 10% palladium on activated charcoal (70mg). After 2 h the mixture was filtered through celite and the solvent was partially
 10 evaporated *in vacuo*. Fumaric acid (6.2mg) was added and the solvent was evaporated *in vacuo* to give a residue. The residue was treated with hot MeOH (10ml) and was filtered. The filtrate was evaporated *in vacuo* to give the *title compound* (48mg). LCMS RT = 3.25min, ES +ve 655 (MH)⁺.

15

Example 28

Synthesis of cyclopentyl 3-[(2-{[6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl]oxy}ethoxy)methyl]phenylcarbamate acetate

20

i) Cyclopentyl 3-[(2-{[6-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl]oxy}ethoxy)methyl]phenylcarbamate

25

A stirred solution of (5R)-3-{6-[2-{[(3-aminophenyl)methyl]oxy}ethoxy]-hexyl}-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (201mg) and diisopropylethylamine (0.54ml) in dichloromethane (10ml) under nitrogen was treated with cyclopentylchloroformate (0.348ml) and the mixture was stirred at 20° for 51 h. Sat.
 25 sodium bicarbonate solution (20ml) was added and the mixture was extracted with dichloromethane (3x20ml). The combined extracts were dried (Na₂SO₄) and the solvent evaporated *in vacuo* to give a residue which was purified by Biotage. Elution with dichloromethane-ethanol-ammonia (275:8:1) gave the *title compound* (100mg). LCMS RT = 3.80min, ES +ve 611 (MH)⁺.

30

ii) Cyclopentyl 3-[(2-{[6-(((2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino)hexyl]oxy}ethoxy)methyl]phenylcarbamate

The *title compound* was prepared by a procedure similar to that described in Example 25 iv). LCMS RT = 3.05min, ES +ve 585 (MH)⁺.

35

iii) Cyclopentyl 3-[(2-{[6-((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]-ethyl)amino]hexyl}oxy)ethoxy)methyl]phenylcarbamate acetate

The *title compound* was prepared by a procedure similar to that described in Example 1xiii). LCMS RT = 2.71min, ES +ve 545 (MH)⁺.

5

Example 29

Synthesis of 5-{3'-[(2-{[6-((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino]hexyl}oxy)ethoxy)methyl]-1,1'-biphenyl-3-yl}pyrimidine-2,4(1H,3H)-dione acetate

10

i) (5R)-3-{6-[2-[(3'-{2,4-bis(1,1-Dimethylethyl)oxy}pyrimidin-5-yl)-1,1'-biphenyl-3-yl]methoxy]ethoxy}hexyl}-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

The *title compound* was prepared by a procedure similar to that described in Example 25 iii). LCMS RT = 4.43min, ES +ve 782 (MH)⁺.

15

ii) (1R)-2-{[6-(2-{[3'-{2,4-bis(1,1-Dimethylethyl)oxy}pyrimidin-5-yl)-1,1'-biphenyl-3-yl]methoxy}ethoxy)hexyl]amino}-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol

The *title compound* was prepared by a procedure similar to that described in Example 21viii). LCMS RT = 3.73min, ES +ve 756 (MH)⁺.

20

iii) 5-{3'-[(2-{[6-((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino]hexyl}oxy)ethoxy)methyl]-1,1'-biphenyl-3-yl}pyrimidine-2,4(1H,3H)-dione acetate

The *title compound* was prepared by a procedure similar to that described in Example 1xiii). LCMS RT = 2.57min, ES +ve 604 (MH)⁺.

25

Example 30

Synthesis of 4-{(1R)-1-hydroxy-2-[(6-{2-[(3-iodobenzyl)oxy]ethoxy}hexyl)amino]-ethyl}-2-(hydroxymethyl)phenol acetate

30

i) 2-{(3-Iodophenyl)methoxy}ethanol

The *title compound* was prepared by a procedure similar to that described in Example 21i). LCMS RT = 2.84min, ES +ve 296 (MNH₄)⁺.

ii) 1-[(2-{[6-Bromohexyl]oxy]ethoxy)methyl]-3-iodobenzene

The *title compound* was prepared by a procedure similar to that described in Example 21ii). LCMS RT = 4.12min.

- 5 iii) (5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-3-{6-[2-[(3-iodophenyl)-methoxy]ethoxy]hexyl}-1,3-oxazolidin-2-one

The *title compound* was prepared by a procedure similar to that described in Example 21iii). LCMS RT = 3.87min, ES +ve 610 (MH)⁺.

- 10 iv) (1R)-1-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-[(6-[2-[(3-iodobenzyl)oxy]ethoxy]hexyl)amino]ethanol

The *title compound* was prepared by a procedure similar to that described in Example 21viii). LCMS RT = 3.07min, ES +ve 584 (MH)⁺.

- 15 v) 4-[(1R)-1-Hydroxy-2-[(6-[2-[(3-iodobenzyl)oxy]ethoxy]hexyl)amino]ethyl]-2-(hydroxymethyl)phenol acetate The *title compound* was prepared by a procedure similar to that described in Example 1xiii). LCMS RT = 2.73min, ES -ve 542 (M-H)⁻.

Example 31

- 20 Synthesis of 3'-[(2-[(6-[(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy]ethoxy)methyl]-1,1'-biphenyl-3-ol acetate

- i) (5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-3-{6-[2-[(3'-hydroxy-1,1'-biphenyl-3-yl)methyl]oxy]ethoxy]hexyl}-1,3-oxazolidin-2-one

- 25 A stirred mixture of (5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-3-{6-[2-[(3-iodophenyl)methyl]oxy]ethoxy]hexyl}-1,3-oxazolidin-2-one (300mg), 3-hydroxyphenylboronic acid (102mg), tripotassium phosphate (417mg) and dichlorobis(triphenylphosphine)palladium(II) (100mg) in dimethoxymethane (10ml) under nitrogen was heated under reflux for 4 h. The mixture was cooled to 20° and diluted with water (50ml). The mixture was extracted with EtOAc (2x25ml) and the
30 combined extracts washed with water (50ml) and dried (Na₂SO₄). Solvent evaporation *in vacuo* gave a residue which was purified by Biotage. Elution with diethyl ether gave the *title compound* (130mg). LCMS RT = 3.74min, ES +ve 593 (MNH₄)⁺.

- 35 ii) 3'-[(2-[(6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino)hexyl]oxy]ethoxy)methyl]-1,1'-biphenyl-3-ol

The *title compound* was prepared by a procedure similar to that described in Example 21viii). LCMS RT = 2.99min, ES +ve 550 (MH)⁺.

5 iii) 3'-[(2-[(6-(((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino)hexyl]oxy)ethoxy)methyl]-1,1'-biphenyl-3-ol acetate

The *title compound* was prepared by a procedure similar to that described in Example 1xiii). LCMS RT = 2.69min, ES +ve 510 (MH)⁺.

The following examples were prepared similarly:

10

Example 32

N-(3-Ethylphenyl)-N'-[3-[(2-[(6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl]oxy)ethoxy)methyl]phenyl]urea acetate
LCMS RT = 3.00 min, ES +ve 580 (MH)⁺.

15

Example 33

N-[3-[(2-[(6-(((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl]oxy)ethoxy)methyl]phenyl]-N'-(3-methylphenyl)urea acetate

20

LCMS RT = 2.73 min, ES +ve 566 (MH)⁺.

Example 34

N-[3-[(2-[(6-(((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl]oxy)ethoxy)methyl]phenyl]-N'-(3-trifluoromethyl)phenyl]urea acetate

25

LCMS RT = 2.91min, ES +ve 620 (MH)⁺.

Example 35

N-(3,5-Dichlorophenyl)-N'-[2-[(2-[(6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl]oxy)ethoxy)methyl]phenyl]urea acetate
LCMS RT = 3.19 min, ES +ve 620, 622, 623 (MH)⁺.

30

Example 36

N-(3-Chlorophenyl)-N'-[3-[(2-[[6-[(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]hexyl]oxy]ethoxy)methyl]phenyl]urea acetate
LCMS RT =3.01 min, ES +ve 586, 588 (MH)⁺.

5 Example 37

N-[3-[(2-[[6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]hexyl]oxy]ethoxy)methyl]phenyl]-N'-(3-iodophenyl)urea acetate LCMS RT =3.12 min, ES +ve 677 (MH)⁺.

10 Example 38

4-[(1R)-2-[(6-[2-[(3-Aminobenzyl)oxy]ethoxy)hexyl]amino]-1-hydroxyethyl]-2-(hydroxymethyl)phenol acetate
LCMS RT =4.32 min, ES +ve 433 (MH)⁺.

15 Example 39

N-[3-[(2-[[6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]hexyl]oxy]ethoxy)methyl]phenyl]pyridine-3-carboxamide acetate
LCMS RT =2.31 min, ES +ve 538 (MH)⁺.

20 Example 40

N-[3-[(2-[[6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]hexyl]oxy]ethoxy)methyl]phenyl]thiophene-2-carboxamide acetate
LCMS RT =2.69 min, ES +ve 543 (MH)⁺.

25 Example 41

N-[3-[(2-[[6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]hexyl]oxy]ethoxy)methyl]phenyl]benzamide acetate
LCMS RT = 2.72min, ES +ve 537 (MH)⁺.

30 Example 42

3-(Benzoylamino)-N-[3-[(2-[[6-[(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]hexyl]oxy]ethoxy)methyl]phenyl]benzamide acetate
LCMS RT = 2.70 min, ES +ve 656 (MH)⁺

35 Example 43

N-{3-[(3-[(2-[6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino]hexyl]oxy)ethoxy)methyl]phenyl}amino)carbonyl]phenyl}thiophene-2-carboxamide acetate

LCMS RT = 2.74 min, ES +ve 662 (MH)⁺.

5

Example 44

N-{3-[(3-[(2-[6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino]hexyl]oxy)ethoxy)methyl]phenyl}amino)carbonyl]phenyl}nicotinamide acetate (1:2)

10 LCMS RT = 2.51min, ES +ve 657 (MH)⁺.

Example 45

N-(3-[(3-[(2-[6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino]hexyl]oxy)ethoxy)methyl]phenyl}amino)carbonyl]amino}phenyl)-benzenesulfonamide

15

LCMS RT = 2.80min, ES +ve 707 (MH)⁺.

Example 46

4-[(1R)-2-[(6-[2-(1,1'-Biphenyl-2-yl)methoxy]ethoxy)hexyl]amino]-1-hydroxyethyl]-2-(hydroxymethyl)phenol acetate

20

LCMS RT = 2.77min, ES +ve 494 (MH)⁺.

Example 47

4-[(1R)-1-Hydroxy-2-[(6-[2-[(4'-methoxy-1,1'-biphenyl-2-yl)methoxy]ethoxy)-hexyl]amino]ethyl]-2-(hydroxymethyl)phenol acetate

25

LCMS RT = 2.79min, ES +ve 524 (MH)⁺.

Example 48

4-[(1R)-2-[(6-[2-[(3-Bromobenzyl)oxy]ethoxy)hexyl]amino]-1-hydroxyethyl]-2-(hydroxymethyl)phenol acetate

30

LCMS RT = 2.68min, ES +ve 498 (MH)⁺.

Example 49

2-(Hydroxymethyl)-4-[(1R)-1-hydroxy-2-[(6-[2-[(3-phenoxybenzyl)oxy]ethoxy)-hexyl]amino]ethyl]phenol acetate

35

LCMS RT = 2.85min, ES +ve 510 (MH)⁺.

Example 50

5 4-((1R)-1-Hydroxy-2-[(6-{2-[(4-hydroxybenzyl)oxy]ethoxy}hexyl)amino]ethyl)-2-(hydroxymethyl)phenol

LCMS RT = 2.40 min, ES +ve 434 (MH)⁺.

Example 51

10 5-[3-[(2-[(6-((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino]hexyl)oxy]ethoxy)methyl]phenyl]pyrimidine-2,4-diol acetate

LCMS RT = 2.19 min, ES +ve 528 (MH)⁺.

Example 52

15 4-((1R)-2-[(6-{2-[(2,5-Dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl)-2-(hydroxymethyl)phenol acetate

LCMS RT = 2.86min, ES +ve 486 (MH)⁺, 488 (MH)⁺.

Example 53

20 4-((1R)-2-[(6-{2-[(3,5-Dimethylbenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl)-2-(hydroxymethyl)phenol acetate

LCMS RT = 2.76min, ES +ve 446 (MH)⁺.

Example 54

25 4-((1R)-2-[(6-{2-[(2-Fluoro-6-(trifluoromethyl)benzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl)-2-(hydroxymethyl)phenol

LCMS RT = 2.65min, ES +ve 504 (MH)⁺.

Example 55

30 2-(Hydroxymethyl)-4-((1R)-1-hydroxy-2-[(6-{2-[(3-(trifluoromethoxy)benzyl]oxy]ethoxy}hexyl)amino]ethyl)phenol acetate

LCMS RT = 2.89min, ES +ve 502 (MH)⁺.

Example 56

35 2-(Hydroxymethyl)-4-((1R)-1-hydroxy-2-[(6-{2-[(2-methyl-1,1'-biphenyl-3-yl)methoxy]ethoxy}hexyl)amino]ethyl)phenol

LCMS RT = 2.89min, ES +ve 508 (MH)⁺.

Example 57

5 3-[(2,3-Dihydroimidazo[2,1-b][1,3]thiazol-6-ylmethyl)amino]-N-{3-[(2-{[6-((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino]hexyl}oxy)ethoxy]-methyl]phenyl}benzamide acetate (1:3) LCMS RT = 2.43 min, ES +ve 690 (MH)⁺.

Example 58

10 N-(3-{[(3-[(2-{[6-((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino]hexyl}oxy)ethoxy)methyl]phenyl}amino)carbonyl]amino}phenyl)benzamide
LCMS RT = 2.80 min, ES +ve 671 (MH)⁺.

Example 59

15 N-(3-{[(3-[(2-{[6-((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino]hexyl}oxy)ethoxy)methyl]phenyl}amino)carbonyl]amino}phenyl)thiophene-2-carboxamide
LCMS RT = 2.80 min, ES +ve 677 (MH)⁺.

Example 60

20 N-(1,1'-Biphenyl-3-yl)-N'-(3-[(2-{[6-((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino]hexyl}oxy)ethoxy)methyl]phenyl)urea
LCMS RT = 3.20 min, ES +ve 628 (MH)⁺.

Example 61

25 N-(3-Aminophenyl)-N'-(3-[(2-{[6-((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino]hexyl}oxy)ethoxy)methyl]phenyl)urea acetate
LCMS RT = 2.38 min, ES +ve 567 (MH)⁺.

Example 62

30 3-[(2-{[6-((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino]-hexyl}oxy)ethoxy)methyl]-N-methylbenzenesulfonamide compound with (2E)-but-2-enedioic acid (2:1)
LCMS RT = 2.25min, ES +ve 511 (MH)⁺.

Example 63

N-{3-[(2-{[6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]-amino]hexyl}oxy)ethoxy)methyl]phenyl}-3-[(thien-2-ylsulfonyl)amino]benzamide
compound with (2E)-but-2-enedioic acid (2:1)

5 LCMS RT = min, 2.72ES +ve 698 (MH)*.

Example 64

N-{3-[(2-{[5-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]-amino]pentyl}oxy)ethoxy)methyl]phenyl}-N'-phenylurea
acetate

10

i) 1-{2-[(5-Bromopentyl)oxy]ethoxy)methyl}-3-nitrobenzene

The *title compound* was prepared by a procedure similar to that described in example 21 ii). LCMS RT = 3.42min

15

ii) (5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-3-(5-{2-[(3-nitrobenzyl)oxy]ethoxy}pentyl)-1,3-oxazolidin-2-one

The *title compound* was prepared by a procedure similar to that described in example 21 iii). LCMS RT = 3.46min

20

iii) (5R)-3-(5-{2-[(3-Aminobenzyl)oxy]ethoxy}pentyl)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

The *title compound* was prepared by a procedure similar to that described in example 21 iv). LCMS RT = 3.13min

25

iv) N-(3-{[2-[(5-[(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]pentyl]oxy)ethoxy)methyl]phenyl}-N'-phenylurea

The *title compound* was prepared by a procedure similar to that described in example 21 v). LCMS RT = 3.58min

30

v) N-[3-{[2-[(5-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]-amino]pentyl]oxy)ethoxy)methyl]phenyl}-N'-phenylurea

The *title compound* was prepared by a procedure similar to that described in example 1 xii). LCMS RT = 2.79min

vi) N-{3-[(2-[(5-[(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl) phenyl]ethyl] amino)pentyl]oxy)ethoxy)methyl]phenyl}-*N'*-phenylurea acetate

The *title compound* was prepared by a procedure similar to that described in example 1

5 xiii). LCMS RT = 2.42min, ES +ve 538 (MH)⁺

Example 65

N-{3-[(3-[(5-[(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl] amino)pentyl]oxy)propoxy)methyl]phenyl}-*N'*-phenylurea acetate

10

i) 3-[(3-Nitrobenzyl)oxy]propan-1-ol

The *title compound* was prepared by a procedure similar to that described in example

21 i). TSP +ve 229 (MH)⁺

15 ii) 1-[(3-[(5-Bromopentyl)oxy]propoxy)methyl]-3-nitrobenzene

The *title compound* was prepared by a procedure similar to that described in example

21 ii). LCMS RT = 3.80min

20 iii) (5*R*)-5-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-3-(5-{3-[(3-nitrobenzyl)oxy] propoxy}pentyl)-1,3-oxazolidin-2-one

The *title compound* was prepared by a procedure similar to that described in example

21 iii) LCMS RT = 3.57min

25 iv) (5*R*)-3-(5-{3-[(3-Aminobenzyl)oxy]propoxy}pentyl)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

The *title compound* was prepared by a procedure similar to that described in example

21 iv). LCMS RT = 3.21min

30 v) N-(3-[(3-[(5-[(5*R*)-5-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]pentyl]oxy)propoxy)methyl]phenyl)-*N'*-phenylurea

The *title compound* was prepared by a procedure similar to that described in example

21 v). LCMS RT = 3.62min

vi) N-[3-[(3-[(5-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino)pentyl]oxy]propoxy)methyl]phenyl]-N'-phenylurea

The *title compound* was prepared by a procedure similar to that described in example 1 xii). LCMS RT = 2.94min

5

vii) N-[3-[(3-[(5-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)pentyl]oxy]propoxy)methyl]phenyl]-N'-phenylurea acetate

The *title compound* was prepared by a procedure similar to that described in example 1 xiii). LCMS RT = 2.50min, ES +ve 552 (MH)⁺

10

Example 66

N-[3-[(2-[(7-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)heptyl]oxy]ethoxy)methyl]phenyl]-N'-phenylurea acetate

15

i) 1-[(2-[(7-Bromoheptyl]oxy)ethoxy)methyl]-3-nitrobenzene

The *title compound* was prepared by a procedure similar to that described in example 21 ii). LCMS RT = 3.83min

20

ii) (5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-3-(7-[2-[(3-nitrobenzyl]oxy]ethoxy]heptyl)-1,3-oxazolidin-2-one

The *title compound* was prepared by a procedure similar to that described in example 21 iii). LCMS RT = 3.67min

25

iii) (5R)-3-(7-[2-[(3-Aminobenzyl]oxy]ethoxy]heptyl)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

The *title compound* was prepared by a procedure similar to that described in example 21 iv). LCMS RT = 3.40min

30

iv) N-[3-[(2-[(7-[(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]heptyl]oxy]ethoxy)methyl]phenyl]-N'-phenylurea

The *title compound* was prepared by a procedure similar to that described in example 21 v). LCMS RT = 3.74min

v) N-[3-({2-[(7-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino)heptyl]oxy}ethoxy)methyl]phenyl]-N'-phenylurea

The *title compound* was prepared by a procedure similar to that described in example 1 xii). LCMS RT = 2.91min

5

vii) N-[3-[(2-[(7-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)heptyl]oxy}ethoxy)methyl]phenyl]-N'-phenylurea acetate

The *title compound* was prepared by a procedure similar to that described in example 1 xiii). LCMS RT = 2.58min, ES +ve 566 (MH)⁺

10

Example 67

N-[3-[(3-[(2-[(5-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)pentyl]oxy}ethoxy)methyl]phenyl]amino)carbonyl]amino)phenyl]nicotinamide acetate

15

i) N-[3-[(2-[(5-[(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]pentyl]oxy}ethoxy)methyl]phenyl]-N'-(3-nitrophenyl)urea

The *title compound* was prepared by a procedure similar to that described in example 21 v) using 3-nitrophenyl isocyanate and purified using Biotage eluting with DCM-MeOH (50:1). LCMS RT = 3.67min

20

ii) N-(3-Aminophenyl)-N'-(3-[(2-[(5-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]pentyl]oxy}ethoxy)methyl]phenyl)urea

The *title compound* was prepared by a procedure similar to that described in example

25

21 iv). LCMS RT = 3.22min

iii) N-[3-[(3-[(2-[(5-[(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]pentyl]oxy}ethoxy)methyl]phenyl]amino)carbonyl]amino)phenyl]nicotinamide

30

The *title compound* was prepared by a procedure similar to that described in example 21 vii). LCMS RT = 3.38min

iv) N-{3-[[[3-[(2-[(5-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino)pentyl]oxy]ethoxy)methyl]phenyl]amino]carbonyl]amino}phenyl]nicotinamide

- 5 The *title compound* was prepared by a procedure similar to that described in example 21 vii). It was purified using Prep. TLC (silica, 1mm thick, 20x20cm) eluting with DCM-EtOH : aqueous ammonia S.G. 0.880 (100:8:1) to yield the *title compound* (83mg).
LCMS RT = 2.73min

10 v) N-(3-[[[3-[(2-[(5-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)pentyl]oxy]ethoxy)methyl]phenyl]amino]carbonyl]amino}phenyl]nicotinamide acetate

The *title compound* was prepared by a procedure similar to that described in example 21 viii) LCMS RT = 2.45min, ES +ve 658 (MH)⁺

15 Example 68

N-(3-[[[3-[(3-[(5-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)pentyl]oxy]propoxy)methyl]phenyl]amino]carbonyl]amino}phenyl]nicotinamide acetate

20 i) N-(3-[[[3-[(5-[(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]pentyl]oxy]propoxy)methyl]phenyl]-N'-(3-nitrophenyl)urea

The *title compound* was prepared by a procedure similar to that described in example 21 v). LCMS RT = 3.75min

25 ii) N-(3-Aminophenyl)-N-(3-[[[3-[(5-[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]pentyl]oxy]propoxy)methyl]phenyl]urea

The *title compound* was prepared by a procedure similar to that described in example 21 iv). LCMS RT = 3.31min

30 iii) N-[3-[[[3-[(3-[(5-[(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]pentyl]oxy]propoxy)methyl]phenyl]amino]carbonyl]amino}phenyl]nicotinamide

The *title compound* was prepared by a procedure similar to that described in example 21 vii). LCMS RT = 3.46min

- 5 iv) N-{3-[[[3-[[3-[[5-[(2*R*)-2-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino]pentyl]oxy]propoxy)methyl]phenyl]amino]carbonyl]amino]phenyl}nicotinamide

The *title compound* was prepared by a procedure similar to that described in example 21 viii) LCMS RT = 2.80min

- 10 v) N-(3-[[[3-[[3-[[3-[(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]pentyl]oxy]propoxy)methyl]phenyl]amino]carbonyl]amino]phenyl)nicotinamide acetate

The *title compound* was prepared by a procedure similar to that described in example 1 xiii). LCMS RT = 2.51min, ES +ve 672 (MH)⁺

15

Example 69

N-(3-[[[3-[[3-[[3-[(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]heptyl]oxy]propoxy)methyl]phenyl]amino]carbonyl]amino]phenyl)nicotinamide acetate

20

- i) N-(3-[[[3-[[7-[(5*R*)-5-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]heptyl]oxy]propoxy)methyl]phenyl)-N'-(3-nitrophenyl)urea

The *title compound* was prepared by a procedure similar to that described in example 21 v). LCMS RT = 3.84min

25

- ii) N-(3-Aminophenyl)-N-(3-[[[3-[[7-[(5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]heptyl]oxy]propoxy)methyl]phenyl)urea

The *title compound* was prepared by a procedure similar to that described in example 21 iv). LCMS RT = 3.44min

30

- iii) N-[3-[[[3-[[3-[[7-[(5*R*)-5-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]heptyl]oxy]propoxy)methyl]phenyl]amino]carbonyl]amino]phenyl]nicotinamide

The *title compound* was prepared by a procedure similar to that described in example 21 vii). LCMS RT = 3.57min

- iv) N-{3-[[[3-[[3-[[7-[[2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino]heptyl]oxy]propoxy)methyl]phenyl]amino}carbonyl]amino]phenyl}nicotinamide

The *title compound* was prepared by a procedure similar to that described in example 21 viii). LCMS RT = 2.83min

- v) N-(3-[[[3-[[3-[[7-[[2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]heptyl]oxy]propoxy)methyl]phenyl]amino}carbonyl]amino]phenyl}nicotinamide acetate

The *title compound* was prepared by a procedure similar to that described in example 1 xiii). LCMS RT = 2.58min, ES +ve 686 (MH)⁺

Example 70

N-{3-[[2-[[5-[[2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]pentyl]oxy]ethoxy)methyl]phenyl}methanesulfonamide acetate

- i) N-(3-[[2-[[5-[[5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]pentyl]oxy]ethoxy)methyl]phenyl}methanesulfonamide

A solution of (5R)-3-(5-(2-[(3-aminobenzyl)oxy]ethoxy)pentyl)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (52mg) in pyridine (4ml) was treated with methanesulfonyl chloride (13mg) at 20°C for 3h. The mixture was quenched with sat. aqueous sodium bicarbonate (20ml) and partitioned with DCM. The organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo*. The residue was purified using SPE eluting with DCM then EtOAc-PE (3:1). The selected fractions were evaporated *in vacuo* to yield the *title compound* (39mg).

LCMS RT = 3.29min

- ii) N-{3-[[2-[[5-[[2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino]pentyl]oxy]ethoxy)methyl]phenyl}methanesulfonamide

The *title compound* was prepared by a procedure similar to that described in example 1 xii). LCMS RT = 2.53min

5 iii) N-{3-[(2-[(5-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)pentyl]oxy)ethoxy)methyl]phenyl}methanesulfonamide acetate

The *title compound* was prepared by a procedure similar to that described in example 1 xiii). LCMS RT = 2.12min, ES +ve 497 (MH)⁺

Example 71

10 N-{3-[(3-[(5-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)pentyl]oxy)propoxy)methyl]phenyl}methanesulfonamide acetate

i) 1-[(3-[(5-Bromopentyl)oxy]propoxy)methyl]-3-nitrobenzene

15 The *title compound* was prepared by a procedure similar to that described in example 24 ii). LCMS RT = 3.80min

ii) (5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-3-(5-{3-[(3-nitrobenzyl)oxy]propoxy}pentyl)-1,3-oxazolidin-2-one

20 The *title compound* was prepared by a procedure similar to that described in example 21 iii). LCMS RT = 3.57min

iii) (5R)-3-(5-{2-[(3-Aminobenzyl)oxy]ethoxy}pentyl)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

25 The *title compound* was prepared by a procedure similar to that described in example 21 iv). LCMS RT = 3.21min

iv) N-(3-[(3-[(5-[(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]pentyl]oxy)propoxy)methyl]phenyl}methanesulfonamide

30 The *title compound* was prepared by a procedure similar to that described in example 70 i) purified using Biotage eluting with EtOAc-PE (3:1).
LCMS RT = 3.26min

v) N-{3-[(3-[(5-[(2*R*)-2-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino)pentyl]oxy]propoxy)methyl]phenyl}methanesulfonamide

The *title compound* was prepared by a procedure similar to that described in example 1 xii). LCMS RT = 2.57min

5

vi) N-{3-[(3-[(5-[(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)pentyl]oxy]propoxy)methyl]phenyl}methanesulfonamide acetate

The *title compound* was prepared by a procedure similar to that described in example 1 xiii). LCMS RT = 2.20min

10

Example 72

N-{3-[(2-[(7-[(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)heptyl]oxy]ethoxy)methyl]phenyl}methanesulfonamide acetate

15

i) N-{3-[(2-[(7-[(5*R*)-5-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]heptyl]oxy]ethoxy)methyl]phenyl}methanesulfonamide

The *title compound* was prepared by a procedure similar to that described in example 70 i). LCMS RT = 3.48min

20

ii) N-{3-[(2-[(7-[(2*R*)-2-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino)heptyl]oxy]ethoxy)methyl]phenyl}methanesulfonamide

The *title compound* was prepared by a procedure similar to that described in example 1 xii). LCMS RT = 2.69min

25

iii) N-{3-[(2-[(7-[(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)heptyl]oxy]ethoxy)methyl]phenyl}methanesulfonamide acetate

The *title compound* was prepared by a procedure similar to that described in example 1 xiii). LCMS RT = 2.28min, ES +ve 525 (MH)⁺

30

Example 73

N-{3-[(2-[(6-[(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy]ethoxy)methyl]phenyl}benzenesulfonamide acetate

i) N-(3-([2-([6-((5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl)]hexyl)oxy)ethoxy)methyl]phenyl)benzenesulfonamide

The *title compound* was prepared by a procedure similar to that described in example 70 i) using benzenesulfonyl chloride and purified using SPE and eluting with DCM-

5 MeOH (300:1) then at 100:1. LCMS RT = 3.51min

ii) N-(3-([2-([6-((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl]oxy)ethoxy)methyl]phenyl)benzenesulfonamide acetate

The *title compound* was prepared by a procedure similar to that described in example 1
 10 xii). The product was purified using SCX-2 cartridge eluting with EtOH then EtOH-2M ammonia in MeOH (9:1). The resulting residue after solvent evaporation was further purified using SPE eluting with DCM then varying ratios of DCM-EtOH-aqueous ammonia S.G. 0.880. The selected fractions were evaporated *in vacuo* to yield the freebase. This was dissolved in AcOH (4ml) then azeotroped with MeOH (3x8ml) to
 15 yield the *title compound* (214mg). LCMS RT = 2.50min, ES +ve 573 (MH)⁺

Example 74

4-((1R)-2-([6-(2-([3-(Dimethylamino)benzyl]oxy)ethoxy)hexyl]amino)-1-hydroxyethyl)-2-(hydroxymethyl)phenol

20

i) (5R)-3-[6-(2-([3-(Dimethylamino)benzyl]oxy)ethoxy)hexyl]-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

A solution of 3-dimethylaminobenzyl alcohol (641mg) in DMF (3ml) under nitrogen was treated with sodium hydride (220mg, 60% in oil) and the mixture stirred at 20° for 15
 25 min. A solution of 2-([6-((5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl)]hexyl)oxy)ethyl methanesulfonate (2.00g) in DMF (5ml) was added and the mixture was stirred at 20° for 21 h. Phosphate buffer solution (15ml, pH6.5) was added, the mixture stirred for 15 min and then extracted with EtOAc. The combined organic layers were washed with water, dried (Na₂SO₄) and the solvent evaporated *in vacuo*. The residue was purified by Biotage (40g). Elution with EtOAc - PE (1:2) gave
 30 the *title compound* (2.125g). LCMS RT = 3.47 min.

ii) (1R)-2-([6-(2-[3-(Dimethylamino)benzyl]oxy)ethoxy)hexyl]amino)-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol

The *title compound* was prepared by a procedure similar to that described in Example 1xii). LCMS RT = 2.38 min.

5

iii) 4-((1R)-2-([6-(2-[3-(dimethylamino)benzyl]oxy)ethoxy)hexyl]amino)-1-hydroxyethyl)-2-(hydroxymethyl)phenol

The *title compound* was prepared by a procedure similar to that described in Example 1xiii). LCMS RT = 2.17 min, ES +ve 461 (MH)⁺

10

Example 75

3-((2-([6-(((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl]oxy)ethoxy)methyl)-N,N,N-trimethylbenzenaminium acetate compound with acetic acid (1:1)

15

i) Benzyl 6-(2-[3-(dimethylamino)benzyl]oxy)ethoxy)hexyl[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]carbamate

A solution of (1R)-2-([6-(2-[3-(dimethylamino)benzyl]oxy)ethoxy)hexyl]amino)-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol (200mg) in dichloromethane (10ml) was treated under nitrogen with diisopropylethylamine (0.09ml) followed by benzyl chloroformate (0.099ml) and the mixture was stirred at 20° for 4 h. Saturated sodium bicarbonate solution was added and the mixture extracted with dichloromethane. The extract was dried (Na₂SO₄) and the solvent evaporated *in vacuo*. The residue was purified by SPE (silica, 10g). Elution with dichloromethane - ethanol - 0.880 ammonia (250:8:1) gave the *title compound* (220mg). LCMS RT = 3.87 min.

25

ii) 3-{12-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]-13-oxo-15-phenyl-2,5,14-trioxa-12-azapentadec-1-yl}-N,N,N-trimethylbenzenaminium iodide

A solution of benzyl 6-(2-[3-(dimethylamino)benzyl]oxy)ethoxy)hexyl[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]carbamate (571mg) in DMF (9ml) was treated with iodomethane (0.09ml) and the mixture was stirred 20° for 16 h. The solvent was evaporated *in vacuo* and the residue was purified by SPE (silica, 10g). Elution with

30

methanol – 0.880 ammonia (19:1) gave the *title compound* (346mg). LCMS RT = 2.79 min.

iii) 3-[(2-[(6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-

5 hydroxyethyl]amino)hexyl]oxy]ethoxy)methyl]-N,N,N-trimethylbenzenaminium iodide

A solution of 3-{12-[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]-13-oxo-15-phenyl-2,5,14-trioxa-12-azapentadec-1-yl}-N,N,N-trimethylbenzenaminium iodide (195mg) in ethanol (15ml) was hydrogenated over 10% palladium on carbon (194mg) for 5 h. The mixture was filtered through celite and the solvent evaporated *in*

10 *vacuo*. The residue was purified by mass directed autopreparative HPLC to give the *title compound* (7mg). LCMS RT = 2.13 min.

iv) 3-[(2-[(6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-

(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy]ethoxy)methyl]-N,N,N-

15 trimethylbenzenaminium acetate compound with acetic acid (1:1)

The *title compound* was prepared by a procedure similar to that described in Example 1xiii). LCMS RT = 1.87 min, ES +ve 475 M⁺

Example 76

20 N-{4-[(2-[(6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-

(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy]ethoxy)methyl]phenyl]-N'-phenylurea acetate

i) (5R)-3-(6-{2-[(4-Bromobenzyl)oxy]ethoxy)hexyl)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

25 A solution of (5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-3-{6-[(2-hydroxyethyl)oxy]hexyl}-1,3-oxazolidin-2-one (2.00g) in DMF (25ml) under nitrogen was treated with sodium hydride (244mg, 60% in oil) and the mixture was stirred at 20° for 15 min. 4-Bromobenzyl bromide (1.40g) was added and the mixture was stirred at 20° for 18 h. Phosphate buffer solution (50ml, pH6.5) and water (50ml) were added and the mixture was extracted with EtOAc. The extract was washed with water, dried (Na₂SO₄) and the solvent evaporated *in vacuo* to give a residue. The residue was purified by

30

chromatography on flash silica gel (40mm diameter column). Elution with EtOAc - PE (1:1) gave the *title compound* (2.125g). LCMS RT = 3.77 min.

ii) (5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-3-{6-[2-({4-

5 [(diphenylmethylene)amino]benzyl}oxy)ethoxy}hexyl)-1,3-oxazolidin-2-one

A mixture of palladium (II) acetate (40mg), racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (166mg) and cesium carbonate (811mg) under nitrogen was treated with toluene (15ml) and benzophenone imine (0.36ml) followed by a solution of (5R)-3-(6-{2-[(4-bromobenzyl)oxy]ethoxy}hexyl)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (1.00g) in toluene (10ml). The stirred mixture was heated to 100° for 18 h. The mixture was cooled to 20°, dichloromethane (25ml) was added and the mixture was filtered. The filtrate was evaporated *in vacuo* and the residue purified by chromatography on flash silica gel (30mm diameter column). Elution with EtOAc - PE (3:2) gave the *title compound* (890mg). LCMS RT = 4.07 min.

15

iii) (5R)-3-(6-[2-[(4-Aminobenzyl)oxy]ethoxy}hexyl)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

A solution of (5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-3-{6-[2-({4-[(diphenylmethylene)amino]benzyl}oxy)ethoxy}hexyl)-1,3-oxazolidin-2-one (860mg) in MeOH (13ml) was treated with sodium acetate (255mg) followed by hydroxylamine hydrochloride (162mg) and the mixture was stirred at 20° for 0.5 h. Phosphate buffer solution (30ml, pH6.5) was added and the mixture was extracted with EtOAc. The combined extracts were dried (Na₂SO₄) and the solvent evaporated *in vacuo*. The residue was purified by SPE (silica, 10g). Elution with EtOAc - cyclohexane (1:1) then (4:1) gave the *title compound* (321mg). LCMS RT = 3.18 min.

25

iv) N-(4-{[2-({6-[(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)ethoxy]methyl}phenyl)-N'-phenylurea

A solution of (5R)-3-(6-{2-[(4-aminobenzyl)oxy]ethoxy}hexyl)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (150mg) in dichloromethane (5ml) under nitrogen was treated with phenyl isocyanate (0.07ml) and the mixture stirred at 20° for 5 h. Isopropyl alcohol (5ml) was added and the solution was stirred for a further 18 h. The solvent was evaporated *in vacuo* and the residue purified by SPE (silica, 10g). Elution

30

with EtOAc - cyclohexane (3:7) then EtOAc gave the *title compound* (159mg). LCMS RT = 3.68 min.

- 5 v) N-[4-((2-((6-((2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl)amino)hexyl)oxy)ethoxy)methyl]phenyl]-N'-phenylurea

The *title compound* was prepared by a procedure similar to that described in Example 1xii). LCMS RT = 3.68 min.

- 10 vi) N-[4-((2-((6-((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl)oxy)ethoxy)methyl]phenyl]-N'-phenylurea acetate

The *title compound* was prepared by a procedure similar to that described in Example 1xiii). LCMS RT = 2.54 min, ES +ve 552 (MH)⁺

15 Example 77

4-((R)-2-[6-[2-(2,6-Dichlorobenzoyloxy)-ethoxy]-hexylamino]-1-hydroxyethyl)-2-hydroxymethyl-phenol

- 20 i) 2-(2,6-Dichlorobenzoyloxy)ethanol

Sodium methoxide (104.4g, 1.93mol) was added portionwise to ethylene glycol (3.74L) under N₂, keeping the temperature below 35°C. After 1-2 h, 2,6-dichlorobenzylbromide (400g, 1.67mol) was added and the mixture heated to 55-60°C for 1 h. On cooling to 20°C water (2.14L) was added and the mixture extracted with ethyl acetate (2.14L). The aqueous layer was separated and extracted twice with ethyl acetate (2.14L, 1.28L).

- 25 The combined organic extracts were washed with water (2.14L) then evaporated to dryness to afford a colourless oil (371.8g) – LC RT = 4min. This may be chromatographed on silica (Biotage) eluting with 10% ethyl acetate in 60/80 petrol to afford the *title compound*.

- 30 ¹H NMR (500MHz, CDCl₃) δ 7.33 (d, 2H, J=8.2Hz), 7.20 (t, 1H, J=8.2Hz), 4.83 (s, 2H), 3.75 (m, 2H), 3.68 (m, 2H), 2.18 (t, 1H, J=6.3Hz)

ii) 2-[2-(6-Bromo-hexyloxy)-ethoxymethyl]-1,3-dichloro-benzene

50% aq NaOH (1.89L), 2-(2,6-dichlorobenzyloxy)ethanol (473.2g), 1,6-dibromohexane (2.44kg, 5eq) and tetrabutylammonium bromide (34.1g, 5mol%) in toluene (1.89L) was heated to 55-60°C for 8-20 h. On cooling water (558mL) and toluene (558mL) were added. The aqueous phase was separated and diluted with water (1L) then back
5 extracted with toluene (1.1L). The combined toluene extracts were washed twice with water (2.2L), then evaporated to dryness on a rotary evaporator. The excess 1,6-dibromohexane was removed using a wiped film evaporator, and the resulting crude product chromatographed on silica (5kg Biotage), eluting with 5% ethyl acetate in petrol 60/80, to give the *title compound* (503.2g) – LC RT = 7.0min.

10 iii) (R)-3-{6-[2-(2,6-Dichlorobenzyloxy)-ethoxy]-hexyl}-5-(2,2-dimethyl-4H-benzo[1,3]dioxin-6-yl)-oxazolidin-2-one

Potassium *tert*-butoxide (4.38g, 39mmol) was added to a solution of (5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (9.3g, 39mmol) in anhydrous
15 DMF (100mL) under N₂ and the reaction stirred for 1 h at ambient temperature. A solution of 2-[2-(6-bromo-hexyloxy)-ethoxymethyl]-1,3-dichloro-benzene (15g, 39mmol) in anhydrous DMF (25mL) was added and the reaction allowed to stir at ambient temperature for 20 h. The reaction mixture was poured into ice/water (350mL) and extracted with ethyl acetate (300mL). The organic layer was separated then washed
20 successively with water/saturated brine (250mL/25mL), water/brine (25mL/10mL) and finally brine (150mL), before drying over sodium sulfate. The solution was concentrated to dryness under vacuum to afford the *title compound* as an oil (21.6g) – LC RT = 6.8min.

25 iv) (R)-2-{6-[2-(2,6-Dichlorobenzyloxy)-ethoxy]-hexylamino}-1-(2,2-dimethyl-4H-benzo[1,3]dioxin-6-yl)-ethanol

The *title compound* was prepared by a procedure similar to that described in Example 4 (ii).

30 (v) 4-((R)-2-{6-[2-(2,6-Dichlorobenzyloxy)-ethoxy]-hexylamino}-1-hydroxyethyl)-2-hydroxymethyl-phenol

1N HCl (295mL) was added to a solution of (R)-2-{6-[2-(2,6-dichlorobenzyloxy)-ethoxy]-hexylamino}-1-(2,2-dimethyl-4H-benzo[1,3]dioxin-6-yl)-ethanol (52g, 0.099mol) in ethanol (312mL), and the reaction stirred at ambient temperature for 1.5 h. Saturated

sodium bicarbonate solution (500mL) was added followed by dichloromethane (500mL). The aqueous layer was separated and extracted with further dichloromethane (500mL). The combined organic solutions were washed with water/brine mixture (500mL/100mL), then evaporated. The residue (50g) was chromatographed on silica (800g, Biotage) eluting with a dichloromethane/ethanol/ammonia mixture (50/8/1), to afford the *title compound* as an oil (35.2g) – LC RT = 4.1min.

¹H NMR (300MHz, MeOH-d₄) δ 7.47 (m, 2H), 7.38 (m, 2H), 7.19 (dd, 1H, J=8.3, 2.3Hz), 6.84 (d, 1H, J=8.3Hz), 4.90 (s, 2H), 4.78 (dd, 1H, J=8.7, 4.5Hz), 4.74 (s, 2H), 3.78 (m, 2H), 3.68 (m, 2H), 3.55 (t, 2H, J=6.4Hz), 2.87 (dd, 1H, J=12.1, 8.7Hz), 2.79 (dd, 1H, J=12.1, 4.5Hz), 2.69 (m, 2H), 1.63 (m, 4H), 1.44 (m, 4H)

Example 78

Salts of 4-((R)-2-{6-[2-(2,6-Dichlorobenzyloxy)-ethoxy]-hexylamino}-1-hydroxyethyl)-2-hydroxymethyl-phenol

i) Triphenylacetate salt

Triphenylacetic acid (1.81g, 1eq) was added to a solution of 4-((R)-2-{6-[2-(2,6-dichlorobenzyloxy)-ethoxy]-hexylamino}-1-hydroxyethyl)-2-hydroxymethyl-phenol (3.28g) in ethanol (20mL) and the mixture heated to 80°C to obtain a solution. The mixture was allowed to cool to ambient temperature, and the resulting product filtered, washed with a little ethanol, then dried *in vacuo* at 50°C to afford the *title compound* as a white crystalline solid (4.3g). m.pt. (DSC) 131.9-134.2°C.

The XRPD pattern of this product is shown in Figure 1.

ii) α-Phenylcinnamate salt

α-Phenylcinnamic acid (0.249g) was added to a solution of 4-((R)-2-{6-[2-(2,6-dichlorobenzyloxy)-ethoxy]-hexylamino}-1-hydroxyethyl)-2-hydroxymethyl-phenol (0.54g) in isopropanol (5mL). The solution was seeded with product and allowed to stir at ambient temperature for 20 h. The product was filtered, washed with a little isopropanol, then dried *in vacuo* at 50°C to afford the *title compound* as a crystalline white solid (0.56g). m.pt. (DSC) 116.1-117.9°C.

The XRPD pattern of this product is shown in Figure 2.

iii) 1-Naphthoate salt

1-Naphthoic acid (0.16g, 0.97mmol) was added to a solution of 4-((R)-2-{6-[2-(2,6-dichlorobenzyloxy)-ethoxy]-hexylamino}-1-hydroxyethyl)-2-hydroxymethyl-phenol (0.46g) in MIBK (5mL) and the resulting suspension warmed to 80°C. The resulting solution was allowed to cool slowly to ambient temperature and left to stir for 20h. The product was filtered, washed with MIBK, then dried *in vacuo* at 50°C to afford the *title compound* as a solid (0.49g). m.pt. (DSC) 91.4-95.2°C. The XRPD pattern of this product is shown in Figure 3.

iv) (R)-Mandelate salt

(R)-Mandelic acid (0.15g) was added to a solution of 4-((R)-2-{6-[2-(2,6-dichlorobenzyloxy)-ethoxy]-hexylamino}-1-hydroxyethyl)-2-hydroxymethyl-phenol (0.48g) in MIBK (5mL) and the resulting suspension warmed to 80°C. The resulting solution was allowed to cool slowly to ambient temperature and left to stir for 20h. The product was filtered, washed with MIBK, then dried *in vacuo* at 50°C to afford the *title compound* as a solid (0.44g). The XRPD pattern of this product is shown in Figure 4.

Example 79

4-((1R)-2-[(5-{2-[(2,6-Dichlorobenzyl)oxy]ethoxy}pentyl)amino]-1-hydroxyethyl)-2-(hydroxymethyl)phenol acetate

i) 2-((2-[(5-Bromopentyl)oxy]ethoxy)methyl)-1,3-dichlorobenzene

Prepared from 2-[(2,6-dichlorobenzyl)oxy]ethanol using method described in Example 77 ii)
LCMS RT=3.91min

ii) (5R)-3-(5-{2-[(2,6-Dichlorobenzyl)oxy]ethoxy}pentyl)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

Prepared using method described in Example 21 iii)
LCMS RT=3.75min

iii) (1R)-2-[(5-{2-[(2,6-Dichlorobenzyl)oxy]ethoxy}pentyl)amino]-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol

Prepared using method described in Example 1 xii)

LCMS RT=2.71min

5

iv) 4-[(1R)-2-[(5-{2-[(2,6-Dichlorobenzyl)oxy]ethoxy}pentyl)amino]-1-hydroxyethyl]-2-(hydroxymethyl)phenol acetate

Prepared using method described in Example 1 xiii)

LCMS RT=2.38min ES+ve 472, 474 and 476 (MH)⁺

10

Example 80

4-[(1R)-2-[(6-{2-[(3-(Cyclopentylsulfonyl)benzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl]-2-(hydroxymethyl)phenol acetate

15

i) Tert-butyl[3-(cyclopentylthio)benzyl]oxydimethylsilane

Tert-butyl[(3-iodobenzyl)oxy]dimethylsilane (WO9513095) (1.44g) in dry 1-methyl-2-pyrrolidone (15ml) and triethylamine (4ml) was stirred at room temperature under nitrogen. 1-1'Bis(diphenylphosphino)ferrocene (110mg) and

20

tris(dibenzylideneacetone)dipalladium(0) (258mg) were added and the mixture was stirred for 15min. Cyclopentyl mercaptan (0.42g) was then added, and the reaction mixture stirred at 60°C for 2h. The reaction mixture was cooled to room temperature, poured onto water and extracted with diethyl ether. The combined organic extracts were dried (MgSO₄) and the solvent evaporated *in vacuo*. The residue was purified on a 50g SPE, eluting with a stepped gradient of 10 to 100% dichloromethane-

25

cyclohexane to give the *title compound* (1.09g) LCMS RT= 4.67min

ii) [3-(Cyclopentylthio)phenyl]methanol

A solution of tetrabutylammonium fluoride in THF (1M, 6ml) was added to a solution of tert-butyl[3-(cyclopentylthio)benzyl]oxydimethylsilane (1.09g) in dry THF (10ml). The solution was stirred for 18h under nitrogen and the solvent was evaporated *in vacuo*.

30

The residue was partitioned between dichloromethane and water. The organic phase was separated and washed with water. The organic phase was separated and the solvent evaporated *in vacuo*. The residue was purified on a 10g silica SPE cartridge,

eluting with a stepped gradient of 10% to 100% dichloromethane- cyclohexane to give the *title compound* (0.65g). LCMS RT= 3.3min

iii) (5R)-3-[6-(2-([3-(Cyclopentylthio)benzyl]oxy)ethoxy)hexyl]-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

5 A solution of [3-(cyclopentylthio)phenyl]methanol (270mg) in dry DMF (10ml) under nitrogen was treated with sodium hydride (60% dispersion on mineral oil, 57mg) and the mixture stirred for 1h. 2-([6-([5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl]oxy)ethyl methanesulfonate (0.4g) in dry DMF (2ml) was then
10 added and the mixture stirred for 18h. Phosphate buffer solution (pH6.5) was added and the mixture extracted with ethyl acetate. The combined extracts were washed with water and dried (MgSO₄), filtered, and evaporated *in vacuo*. The residue was purified on a 10g silica SPE cartridge, eluting with 10% to 20% ethyl acetate- cyclohexane to give the *title compound* (0.23g). LCMS RT= 4.08min.

15

iv) (5R)-3-[6-(2-([3-(Cyclopentylsulfinyl)benzyl]oxy)ethoxy)hexyl]-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

Sodium periodate (333mg) was added to a solution of (5R)-3-[6-(2-([3-(cyclopentylthio)benzyl]oxy)ethoxy)hexyl]-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (230mg) in ethanol (12ml) and water (4ml). The mixture was stirred at
20 room temperature under nitrogen for 3h. and the ethanol evaporated *in vacuo*. The aqueous phase was diluted with water and extracted with ethyl acetate. The combined ethyl acetate extracts were dried (MgSO₄) filtered, and evaporated *in vacuo*. The residue was purified on a 10g silica SPE cartridge, eluting with a stepped gradient of
25 10% to 100% ethyl acetate- cyclohexane, to give the *title compound* (201mg). LCMS RT=3.54min.

v) (5R)-3-[6-(2-([3-(Cyclopentylsulfonyl)benzyl]oxy)ethoxy)hexyl]-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

30 3-Chloroperbenzoic acid (60mg;57%purity) was added to a solution of (1R)-2-([6-(2-([3-([5R)-3-[6-(2-([3-(cyclopentylsulfinyl)benzyl]oxy)ethoxy)hexyl]-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (106mg) in dry DCM (5ml) stirring under nitrogen at 0°C. The solution was allowed to warm up to room temperature and stirred for 2.5h.

The reaction mixture was quenched with aqueous sodium sulphite solution. The organic layer was separated and washed twice with aqueous sodium sulphite, dried (MgSO₄) filtered and evaporated *in vacuo*. The residue was purified on a 5g silica SPE cartridge, eluting with a stepped gradient of 20% to 100% ethyl acetate - cyclohexane to give the *title compound* (96mg). LCMS RT= 3.68min.

vi) (1R)-2-[[6-(2-[[3-(Cyclopentylsulfonyl)benzyl]oxy]ethoxy)hexyl]amino]-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)]ethanol

The *title compound* was prepared from (5R)-3-[6-(2-[[3-(cyclopentylsulfonyl)benzyl]oxy]ethoxy)hexyl]-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one by a procedure similar to that described in example 4ii. The residue was purified on a SPE cartridge, eluting with methanol- dichloromethane-ammonia (10:90:1), to give the *title compound*. LCMS RT = 2.80min.

vii) 4-((1R)-2-[[6-(2-[[3-(Cyclopentylsulfonyl)benzyl]oxy]ethoxy)hexyl]amino]-1-hydroxyethyl)-2-(hydroxymethyl)phenol acetate

The *title compound* was prepared from (1R)-2-[[6-(2-[[3-(cyclopentylsulfonyl)benzyl]oxy]ethoxy)hexyl]amino]-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol, by a procedure similar to that described in example 4iii. LCMS RT= 2.41min. ES+ve 548 (M+H)⁺

Example 81

4-((1R)-2-[[6-(2-[[3-(Cyclopentylsulfinyl)benzyl]oxy]ethoxy)hexyl]amino]-1-hydroxyethyl)-2-(hydroxymethyl)phenol acetate

i) (1R)-2-[[6-(2-[[3-(Cyclopentylsulfinyl)benzyl]oxy]ethoxy)hexyl]amino]-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)]ethanol
The *title compound* was prepared from (5R)-3-[6-(2-[[3-(cyclopentylsulfinyl)benzyl]oxy]ethoxy)hexyl]-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (example 80iv) by a procedure similar to that described in example 4 ii) LCMS RT= 2.69min.

ii) 4-((1R)-2-[[6-(2-[[3-(Cyclopentylsulfinyl)benzyl]oxy]ethoxy)hexyl]amino]-1-hydroxyethyl)-2-(hydroxymethyl)phenol acetate

The *title compound* was prepared from (1R)-2-[[6-(2-[[3-(cyclopentylsulfinyl)benzyl]oxy]ethoxy)hexyl]amino]-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol by a procedure similar to that described in example 4 iii). LCMS RT= 2.43min ES+ve 534 (M+H)⁺

5

Example 82

4-((1R)-2-[[6-(2-[[3-(Cyclopentylthio)benzyl]oxy]ethoxy)hexyl]amino]-1-hydroxyethyl)-2-(hydroxymethyl)phenol acetate

10 i) (1R)-2-[[6-(2-[[3-(Cyclopentylthio)benzyl]oxy]ethoxy)hexyl]amino]-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol

The title compound was prepared from (5R)-3-[6-(2-[[3-(cyclopentylthio)benzyl]oxy]ethoxy)hexyl]-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one by a procedure similar to that described in example 4 ii). LCMS RT= 3.18min

15

ii) 4-((1R)-2-[[6-(2-[[3-(Cyclopentylthio)benzyl]oxy]ethoxy)hexyl]amino]-1-hydroxyethyl)-2-(hydroxymethyl)phenol acetate

The title compound was prepared from (1R)-2-[[6-(2-[[3-(cyclopentylthio)benzyl]oxy]ethoxy)hexyl]amino]-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol by a procedure similar to that described in example 4 iii). LCMS RT= 2.82min ES+ve m/z= 518 (M+H)⁺

20

BIOLOGICAL ACTIVITY

The potencies of the aforementioned compounds were determined using frog melanophores transfected with the human beta 2 adrenoreceptor. The cells were
5 incubated with melatonin to induce pigment aggregation. Pigment dispersal was induced by compounds acting on the human beta 2 adrenoreceptor. The beta 2 agonist activity of test compounds was assessed by their ability to induce a change in light transmittance across a melanophore monolayer (a consequence of pigment dispersal). At the human beta 2 adrenoreceptor, compounds of examples 1 and 4 to 82 had IC₅₀
10 values below 1 μ M.

Potency at human beta1 and beta3 adrenoreceptors was determined in functional studies using Chinese hamster ovary cells transfected with either the human beta1
15 adrenoreceptor or the human beta3 adrenoreceptor. Agonist activity was assessed by measuring changes in intracellular cyclic AMP. For particularly preferred compounds of the invention, selectivity for beta2 adrenoreceptors over beta1 adrenoreceptors was typically 10 fold or greater. Selectivity for beta2 adrenoreceptors over beta3
adrenoreceptors was typically 5 fold or greater.

20 The onset of action and duration of action *in vitro* was assessed on isolated superfused airway preparations (human or guinea pig). Tissues were contracted either electrically or by spasmogen. Agonist was perfused over the tissue until maximum relaxation was achieved, and onset of action determined. Perfusion of the agonist was then ceased and duration determined by the time taken for the contractile response to re-establish.
25 For particularly preferred compounds of the invention, onset was typically less than 30min. Duration was typically >3h.

Particularly preferred compounds of the invention are potent and long-acting inhibitors of histamine-induced bronchospasm in conscious guinea pigs. They also demonstrate
30 an improved therapeutic index in conscious guinea pigs (bronchoprotective effects vs blood pressure lowering effects) relative to established long-acting beta2 agonist bronchodilators.

The particularly preferred compounds of the invention show low oral bioavailability in rat and dog. In human hepatocyte cultures they are metabolised to products that are significantly less potent at the beta2 adrenoceptor than the parent compound.

5

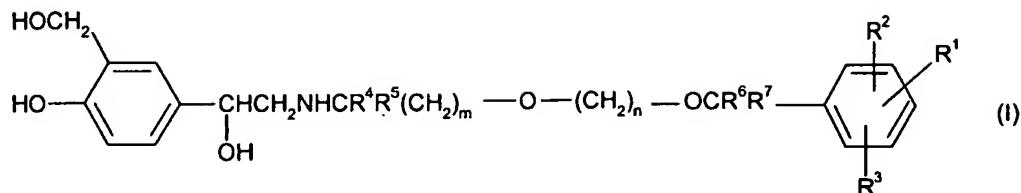
The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may

10

include, by way of example and without limitation, the following claims:

Claims

1. A compound of formula (I)



5

or a salt, solvate, or physiologically functional derivative thereof, wherein:

m is an integer of from 2 to 8;

10

n is an integer of from 2 to 5;

with the proviso that m + n is 4 to 10;

15

R¹ is selected from hydrogen, C₁₋₆alkyl, hydroxy, halo, C₁₋₆haloalkyl, -XC(O)NR⁹R¹⁰, -XNR⁸C(O)R⁹, -XNR⁸C(O)NR⁹R¹⁰, -XNR⁸SO₂R⁹, -XSO₂NR¹¹R¹², XNR⁸SO₂R⁹R¹⁰, -XNR⁹R¹⁰, XN⁺R⁸R⁹R¹⁰, -XNR⁸C(O)OR⁹, -XCO₂R⁹, -XNR⁸C(O)NR⁸C(O)NR⁹R¹⁰, -XSR⁹, XSOR⁹, and -XSO₂R⁹;

20

or R¹ is selected from -X-aryl, -X-hetaryl, and -X-(aryloxy), each optionally substituted by 1 or 2 groups independently selected from hydroxy, C₁₋₆alkoxy, halo, C₁₋₆alkyl, C₁₋₆haloalkyl, -NHC(O)(C₁₋₆alkyl), -SO₂(C₁₋₆alkyl), -SO₂(aryl), -SO₂NH₂, -SO₂NH(C₁₋₆alkyl), -SO₂NH(C₃₋₇cycloalkyl), -CO₂H, -CO₂(C₁₋₆alkyl), -SO₂NH(C₃₋₇cycloalkylC₁₋₆alkyl), -NH₂, -NH(C₁₋₆alkyl), or hetaryl optionally substituted by 1 or 2 groups independently selected from hydroxy, C₁₋₆alkoxy, halo, C₁₋₆alkyl, or C₁₋₆haloalkyl;

25

X is -(CH₂)_p- or C₂₋₆ alkenylene;

p is an integer from 0 to 6,

30

R⁸ and R⁹ are independently selected from hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, aryl, hetaryl, hetaryl(C₁₋₆alkyl)- and aryl(C₁₋₆alkyl)- and R⁸ and R⁹ are each independently optionally substituted by 1 or 2 groups independently selected from halo, C₁₋₆alkyl,

C₁₋₆haloalkyl, -NHC(O)(C₁₋₆alkyl), -SO₂(C₁₋₆alkyl), -SO₂(aryl), -CO₂H, -CO₂(C₁₋₄alkyl), -NH₂, -NH(C₁₋₆alkyl), aryl(C₁₋₆alkyl)-, aryl(C₂₋₆alkenyl)-, aryl(C₂₋₆alkynyl)-, hetaryl(C₁₋₆alkyl)-, -NHSO₂aryl, -NH(hetarylC₁₋₆alkyl), -NHSO₂hetaryl, -NHSO₂(C₁₋₆alkyl), -NHC(O)aryl, or -NHC(O)hetaryl:

5

R¹⁰ is selected from hydrogen, C₁₋₆alkyl and C₃₋₇ cycloalkyl;

R¹¹ and R¹² are independently selected from hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, aryl, hetaryl, hetaryl(C₁₋₆alkyl)- and aryl(C₁₋₆alkyl)-, or R¹¹ and R¹², together with the nitrogen to which they are bonded, form a 5-, 6-, or 7- membered nitrogen containing ring; and R¹¹ and R¹² are each optionally substituted by one or two groups independently selected from halo, C₁₋₆alkyl, and C₁₋₆haloalkyl;

10

where R¹ is -XNR⁸C(O)NR⁹R¹⁰, R⁸ and R⁹ may, together with the -NC(O)N- portion of the group R¹ to which they are bonded, form a 5-, 6- or 7- membered saturated or unsaturated ring;

15

where R¹ is -XNR⁸C(O)OR⁹, R⁸ and R⁹ may, together with the -NC(O)O- portion of the group R¹ to which they are bonded, form a 5-, 6- or 7- membered saturated or unsaturated ring;

20

where R¹ is -XC(O)NR⁹R¹⁰ or -XNR⁸C(O)NR⁹R¹⁰, R⁹ and R¹⁰ may, together with the nitrogen to which they are bonded, form a 5-, 6-, or 7- membered nitrogen containing ring;

25

R² is selected from hydrogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, halo, aryl, aryl(C₁₋₆alkyl)-, C₁₋₆haloalkoxy, and C₁₋₆ haloalkyl;

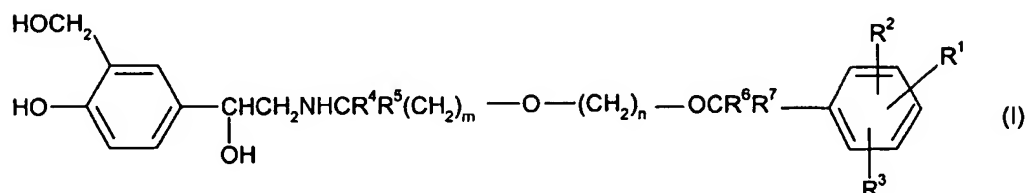
R³ is selected from hydrogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, halo, aryl, aryl(C₁₋₆alkyl)-, C₁₋₆haloalkoxy, and C₁₋₆haloalkyl;

30

R⁴ and R⁵ are independently selected from hydrogen and C₁₋₄ alkyl with the proviso that the total number of carbon atoms in R⁴ and R⁵ is not more than 4; and,

R^6 and R^7 are independently selected from hydrogen and C_{1-4} alkyl with the proviso that the total number of carbon atoms in R^4 and R^5 is not more than 4.

5 2. A compound of formula (I)



or a salt, solvate, or physiologically functional derivative thereof, wherein:

10

m is an integer of from 2 to 8;

n is an integer of from 2 to 5;

with the proviso that $m + n$ is 4 to 10;

15

R^1 is selected from hydrogen, C_{1-6} alkyl, hydroxy, halo, C_{1-6} haloalkyl, $-XC(O)NR^9R^{10}$, $-XNR^8C(O)R^9$, $-XNR^8C(O)NR^9R^{10}$, $-XNR^8SO_2R^9$, $-XSO_2NR^{11}R^{12}$, $-XNR^9R^{10}$, $-XNR^8C(O)OR^9$,

or R^1 is selected from $-X$ -aryl, $-X$ -hetaryl, or $-X$ -(aryloxy), each optionally substituted by 1 or 2 groups independently selected from hydroxy, C_{1-6} alkoxy, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, $-NHC(O)(C_{1-6}alkyl)$, $-SO_2(C_{1-6}alkyl)$, $-SO_2(aryl)$,

20

$-SO_2NH_2$, $-SO_2NH(C_{1-6}alkyl)$, $-SO_2NH(C_{3-7}cycloalkyl)$, $-CO_2H$, $-CO_2(C_{1-6}alkyl)$,

$-SO_2NH(C_{3-7}cycloalkylC_{1-6}alkyl)$, $-NH_2$, $-NH(C_{1-6}alkyl)$, or hetaryl optionally substituted by 1 or 2 groups independently selected from hydroxy, C_{1-6} alkoxy, halo, C_{1-6} alkyl, or C_{1-6} haloalkyl;

25

X is $-(CH_2)_p-$ or C_{2-6} alkenylene;

p is an integer from 0 to 6, preferably 0 to 4;

30

R^8 and R^9 are independently selected from hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, hetaryl, hetaryl($C_{1-6}alkyl$)- and aryl($C_{1-6}alkyl$)- and R^8 and R^9 are each independently

optionally substituted by 1 or 2 groups independently selected from halo, C₁₋₆alkyl, C₁₋₆haloalkyl, -NHC(O)(C₁₋₆alkyl), -SO₂(C₁₋₆alkyl), -SO₂(aryl), -CO₂H, and -CO₂(C₁₋₄alkyl), -NH₂, -NH(C₁₋₆alkyl), aryl(C₁₋₆alkyl)-, aryl(C₂₋₆alkenyl)-, aryl(C₂₋₆alkynyl)-, hetaryl(C₁₋₆alkyl)-, -NHSO₂aryl, -NH(hetarylC₁₋₆alkyl), -NHSO₂hetaryl, -NHSO₂(C₁₋₆alkyl), -NHC(O)aryl, or -NHC(O)hetaryl:

R¹⁰ is selected from hydrogen, C₁₋₆alkyl and C₃₋₇ cycloalkyl;

R¹¹ and R¹² are independently selected from hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, aryl, hetaryl, hetaryl(C₁₋₆alkyl)- and aryl(C₁₋₆alkyl)-, or R¹¹ and R¹², together with the nitrogen to which they are bonded, form a 5-, 6-, or 7- membered nitrogen containing ring; and R¹¹ and R¹² are each optionally substituted by one or two groups independently selected from halo, C₁₋₆alkyl, and C₁₋₆haloalkyl;

where R¹ is -XNR⁸C(O)NR⁹R¹⁰, R⁸ and R⁹ may, together with the portion -NC(O)N- of the group R¹ to which they are bonded, form a 5-, 6-, or 7- membered saturated or unsaturated ring;

where R¹ is -XNR⁸C(O)OR⁹, R⁸ and R⁹ may, together with the portion -NC(O)O- of the group R¹ to which they are bonded, form a 5-, 6-, or 7- membered saturated or unsaturated ring;

where R¹ is -XC(O)NR⁹R¹⁰ or -XNR⁸C(O)NR⁹R¹⁰, R⁹ and R¹⁰ may, together with the nitrogen to which they are bonded, form a 5-, 6-, or 7- membered nitrogen containing ring;

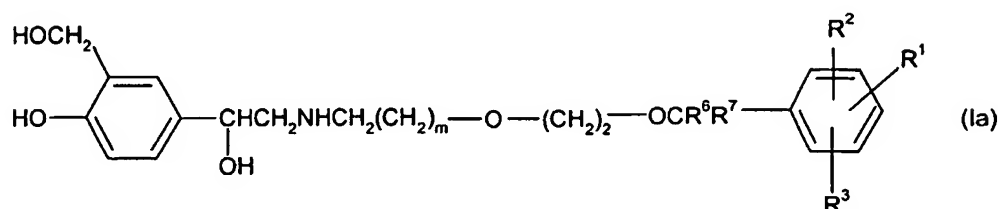
R² is selected from hydrogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, halo, aryl, aryl(C₁₋₆alkyl)-, C₁₋₆haloalkoxy, and C₁₋₆ haloalkyl;

R³ is selected from hydrogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, halo, aryl, aryl(C₁₋₆alkyl)-, C₁₋₆haloalkoxy, and C₁₋₆haloalkyl;

R⁴ and R⁵ are independently selected from hydrogen and C₁₋₄ alkyl with the proviso that the total number of carbon atoms in R⁴ and R⁵ is not more than 4; and,

R^6 and R^7 are independently selected from hydrogen and C_{1-4} alkyl with the proviso that the total number of carbon atoms in R^4 and R^5 is not more than 4.

- 5 3. A compound according to claim 1 or claim 2 of formula (Ia)



- 10 or a salt, solvate, or physiologically functional derivative thereof, wherein R^1 , R^2 , R^3 , R^6 and R^7 are as defined for claim 1 and m is 4 or 5.

4. A compound according to any of claims 1 to 3 which is selected from:
- 15 N-{3-[(2-[(6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino)hexyl]oxy)ethoxy)methyl]phenyl}-N'-phenylurea;
- 4-((1R)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl)-2-(hydroxymethyl)phenol;
- 20 N-(3-(((3-[(2-[(6-(((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino)hexyl]oxy)ethoxy)methyl]phenyl)amino)carbonyl]amino)phenyl)pyridine-3-carboxamide;
- 4-((1R)-1-Hydroxy-2-[(6-{2-[(3-hydroxybenzyl)oxy]ethoxy}hexyl)amino]ethyl)-2-(hydroxymethyl)phenol;
- 4-((1R)-2-[(6-{2-[(3,5-Dimethylbenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl)-2-(hydroxymethyl)phenol;
- 25 N-{3-[(2-[(5-(((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino)pentyl]oxy)ethoxy)methyl]phenyl}-N'-phenylurea;

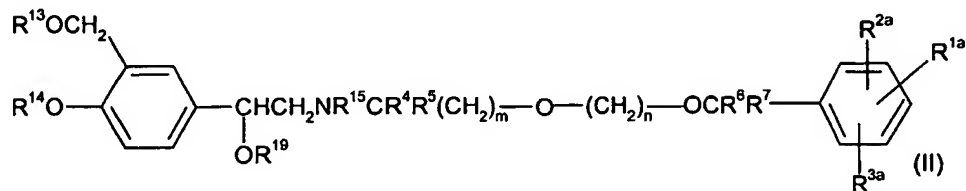
and salts, solvates, and physiologically functional derivatives thereof.

- 30 5. A compound of formula (I) which is:

4-((1*R*)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl)-2-(hydroxymethyl)phenol;
or a salt or solvate thereof.

- 5 6. A pharmaceutical formulation comprising a compound of formula (I) or (Ia) according to any one of claims 1 to 5 or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.
- 10 7. A combination comprising a compound of formula (I) or (Ia) according to any one of claims 1 to 5 or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and one or more other therapeutic ingredients.
- 15 8. A combination according to claim 7 wherein the other therapeutic ingredient is a PDE4 inhibitor, a corticosteroid or an anti-cholinergic agent.
- 20 9. A combination according to claim 7 wherein the additional therapeutic ingredient is 6 α ,9 α -difluoro-17 α -[(2-furanylcarbonyl)oxy]-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid *S*-fluoromethyl ester.
- 25 10. The use of a compound of formula (I) or (Ia) according to any one of claims 1 to 5, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a selective β_2 -adrenoreceptor agonist is indicated.
- 30 11. A method for the prophylaxis or treatment of a clinical condition in a mammal, for which a selective β_2 -adrenoreceptor agonist is indicated, which comprises administration of a therapeutically effective amount of a compound of formula (I) or (Ia) according to any one of claims 1 to 5, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.
- 35 12. A compound of formula (I) or (Ia) according to any one of claims 1 to 5 or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for use in medical therapy.

13. A process for preparing a compound of formula (I) or (Ia) which comprises:
deprotection of a protected intermediate of formula (II):

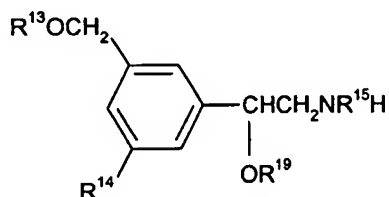


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or a salt or solvate thereof, wherein R^4 , R^5 , R^6 , R^7 , m , and n are as defined for the compound of formula (I) or (Ia), and R^{1a} , R^{2a} , and R^{3a} are each independently either the same as R^1 , R^2 , and R^3 respectively as defined for the compound of formulae (I) or (Ia) or a precursor for said group R^1 , R^2 , or R^3 , and R^{13} , R^{14} , and R^{15} are each independently
10 either hydrogen or a protecting group provided that at least one of R^{13} , R^{14} , and R^{15} is a protecting group, and R^{19} is hydrogen or a protecting group.

(B) alkylation of an amine of formula (XIX):

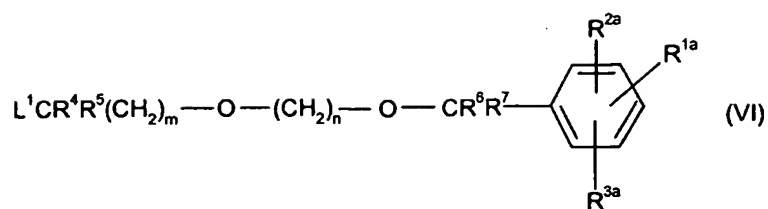
15



(XIX)

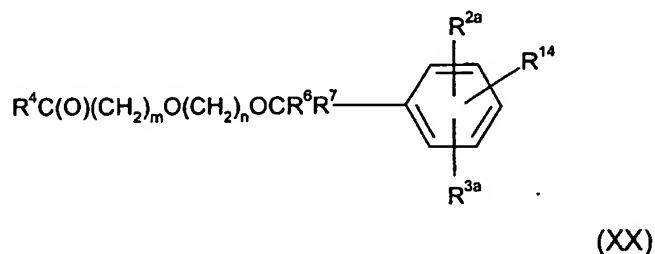
wherein R^{13} , R^{14} , R^{15} and R^{19} are as hereinbefore defined,
with a compound of formula (VI):

108



5 wherein L^1 represents a leaving group such as halo, followed by removal of any protecting groups present by conventional methods.

(C) by reacting an amine of formula (XIX) as defined hereinabove, with a compound of formula (XX):



10

wherein R^4 , R^6 , R^7 , R^{1a} , R^{2a} , R^{3a} , m and n are as hereinbefore defined; under conditions suitable to effect reductive amination,

followed where necessary or desired by one or more of the following steps in any order:

- 15 (i) optional removal of any protecting groups;
- (ii) optional separation of an enantiomer or diastereoisomer from a mixture of enantiomers or diastereoisomers;
- (iii) optional conversion of the product to a corresponding salt, solvate, or physiologically functional derivative thereof.
- 20 (iv) optional conversion of a group R^{1a} , R^{2a} and/or R^{3a} to a group R^1 , R^2 and/or R^3 respectively.

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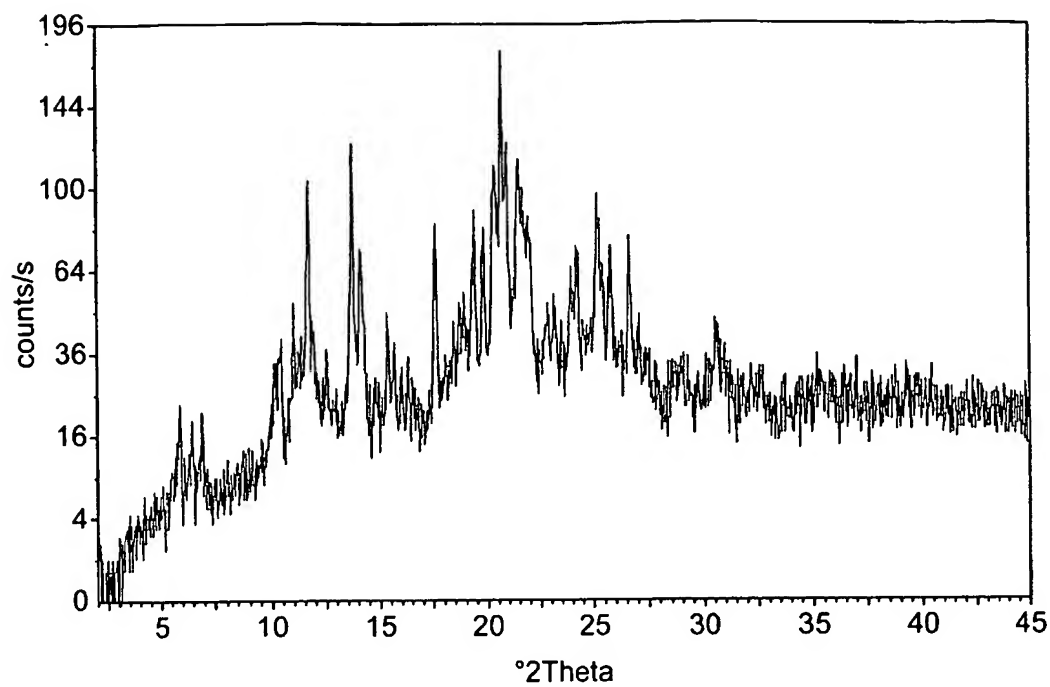


FIG. 1

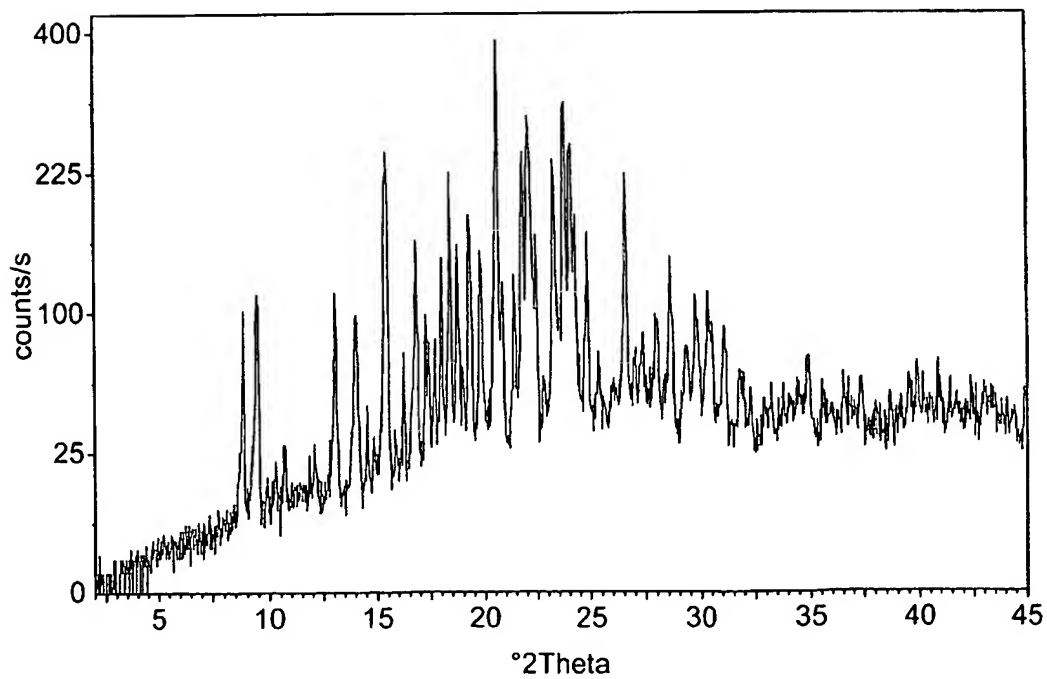


FIG. 2

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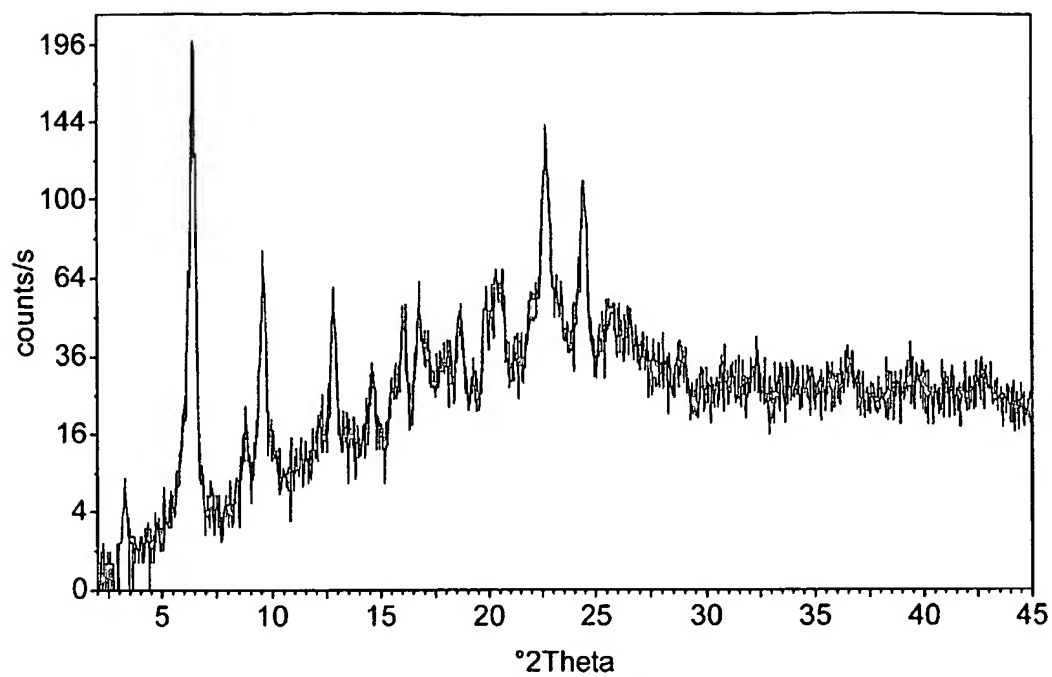


FIG. 3

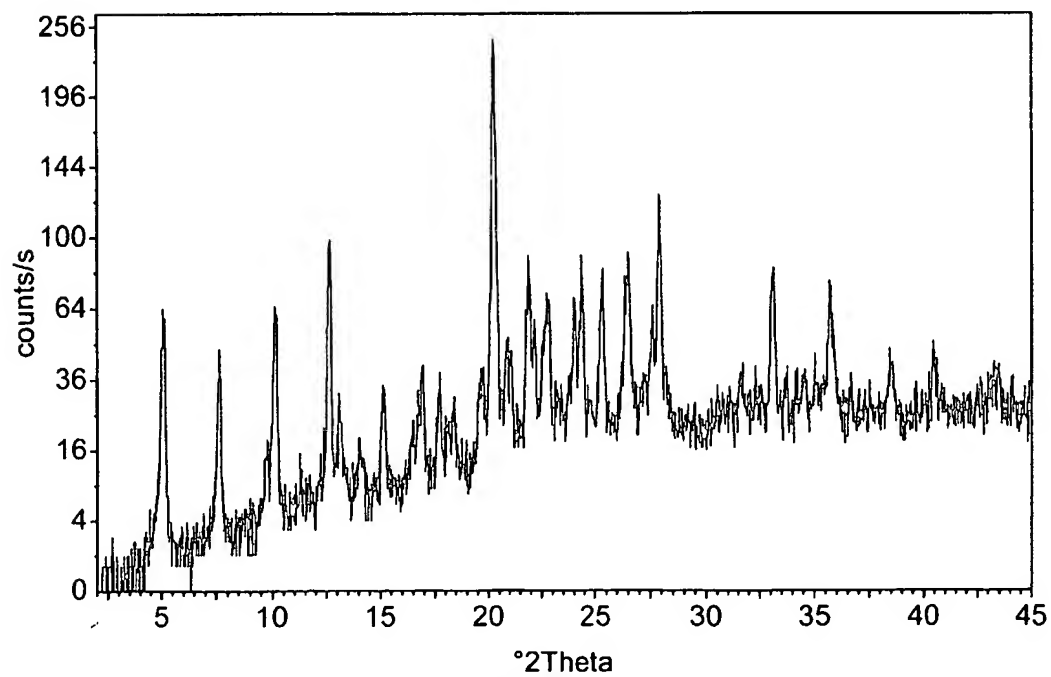


FIG. 4

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/04140

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/133 C07C275/32 C07C217/08 C07C311/29 A61P11/06
C07C317/14 C07C311/08 C07D213/82 C07C311/21 C07D513/04
C07C271/38 C07D239/54 C07D333/38 C07C233/75 C07C237/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GB 2 140 800 A (GLAXO GROUP LTD) 5 December 1984 (1984-12-05) cited in the application page 2, line 62 -page 3, line 10; claims 1,9-11	1-13
Y	EP 0 286 242 A (GLAXO GROUP LTD) 12 October 1988 (1988-10-12) page 7, line 34 - line 40; claim 1; example 12	1-13
Y	EP 0 317 206 A (GLAXO GROUP LTD) 24 May 1989 (1989-05-24) page 5, line 57 -page 6, line 4; claim 1	1-13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *8* document member of the same patent family

Date of the actual completion of the international search

14 November 2002

Date of mailing of the international search report

20/11/2002

Name and mailing address of the ISA

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Seymour, L

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 02/04140

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C275/40 C07D333/34 C07C217/76 C07C317/22 C07C325/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

☐

Further documents are listed in the continuation of box C.

☒

Patent family members are listed in annex.

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P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

B document member of the same patent family

Date of the actual completion of the international search

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Authorized officer

Seymour, L

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 02/04140

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 11 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box I.2

The present claims do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The functional term "physiologically functional derivative" does not enable the skilled person to determine which technical features are necessary to perform the stated function. It is thus unclear which specific compounds fall within the scope of said claim. A lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search does not include "physiologically functional derivatives" of the compounds of formula I.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 02/04140

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 02/04140

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